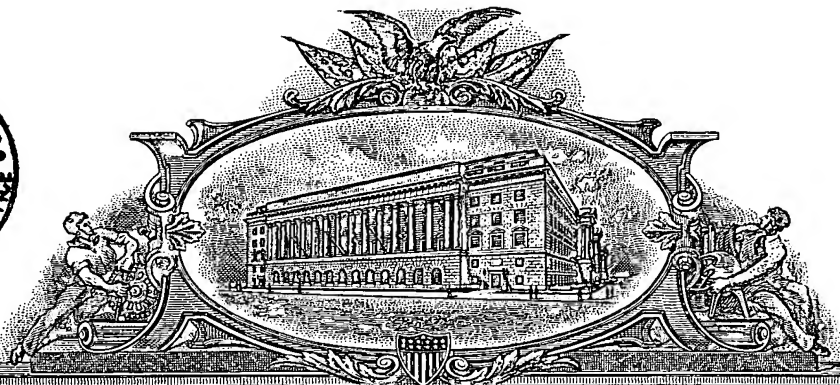




PA 551512



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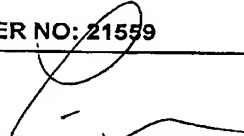
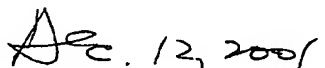
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| Date of Deposit <u>December 12, 2001</u>  | Label Number: <u>EV040971750US</u>                                    |
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10/020683  
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| UTILITY PATENT APPLICATION TRANSMITTAL UNDER 37 C.F.R. § 1.53(b)  |  |
|---|--|
| Attorney Docket Number  | 50125/041001                                     |
| Applicant   | Andrea Aschenbrenner et al.                      |
| Title   | COMPOUNDS FOR THE TREATMENT OF PROTOZOAL DISEASE |
| <b>PRIORITY INFORMATION:</b>  |  |
| This application claims priority from prior foreign patent application DE 101 09 204.0, filed February 26, 2001, in Germany.  |  |
| <b>SMALL ENTITY STATUS:</b>   |  |
| <input type="checkbox"/> Applicant claims small entity status under 37 C.F.R. § 1.27.   |  |
| <b>APPLICATION ELEMENTS:</b>  |  |
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| Specification   | 49 pages   |
| Claims  | 7 pages  |
| Abstract  | 1 pages  |
| Drawing   | 0 sheets   |
| Combined Declaration and POA, which is:<br><input type="checkbox"/> Unsigned  | 5 pages  |
| Sequence Statement  | 0 pages  |
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| Sequence Listing on Diskette  | 0 disk   |
| Small Entity Statement, which is:<br><input type="checkbox"/> A copy from prior application [**SERIAL NUMBER**] and such small entity status is still proper and desired. | 0 pages  |
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| Form PTO 1449   | 0 pages  |

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| <ul style="list-style-type: none"> <li>■ Enclosed is a check for \$1596.00 to cover the total fees.</li> <li>■ Please apply any other charges, or any credits, to Deposit Account No. 03-2095.</li> </ul> |  |
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| <br>Signature Paul T. Clark, Reg. 30,162 for Karen L. Elbing  | <br>Date |

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| <u>Guy E. Beardsley</u><br>Printed name of person mailing correspondence   | <u><i>Guy E. Beardsley</i></u><br>Signature of person mailing correspondence |

APPLICATION  
FOR  
UNITED STATES LETTERS PATENT

APPLICANT : Andrea Aschenbrenner, Katharina Aulinger Fuchs, Matthias Dormeyer, Gabriel Garcia, Bernd Kramer, Stefano Pegoraro, Jürgen Kraus, Rolf Krauss, Hans Leban, Wael Saeb, and Kristina Wolf

TITLE : COMPOUNDS FOR THE TREATMENT OF PROTOZOAL DISEASES

## Compounds for the treatment of protozoal diseases

The present invention relates to compounds which are suitable for the treatment of diseases caused by protozoa, to processes for the preparation of these compounds, and to their use.

DE-A-2 334 355 discloses diphenylurea derivatives which are employed as medicaments against protozoa, in particular against coccidiosis, as said to be superior to the action of 4,4'-dinitrodiphenylurea (nicarbazine), which is furthermore known. DE-A-2 928 485 discloses urea derivatives which are employed for the treatment of disorders of lipid metabolism, WO 96/39382 discloses similar urea derivatives which are employed for treating 5-HT mediated diseases and WO 97/29743, US 5780483 discloses similar urea derivatives which are employed for the treatment of diseases mediated by chemokines. GB 888,965 discloses certain diamidines which are employed for the treatment of protozoal diseases, in particular of babesiasis. The synthesis of certain benzamidines is disclosed in Biochemistry, 1998, 37(48), 17068-81, in Khim.-Farm. Zh., 1974, 8(6), 17-20, and in Bull. Soc. Chim. Fr., 1968, (1), 376-82. Other relevant literature is US 6180675, WO 99/06354, WO 96/25157, WO 99/32463, WO 98/52558, WO 99/32110, GB 755036, US 2762742, US 4405644, WO 00/72840 and WO 94/22807.

The diseases caused by protozoa also include diseases caused by plasmodia (malarial parasites). It is assumed that at present several hundreds of millions of people are suffering from malaria and the number of cases of malaria is likely to increase still further in the next few years, since at present effective methods for the control of malaria are not known. Medicaments which were employed until now against malaria have largely lost their efficacy, as the malarial parasites have become resistant. There is therefore an urgent need for novel medicaments for the prophylactic and curative treatment of malaria. At the same time, the development of novel medicaments against malaria has proved very difficult.

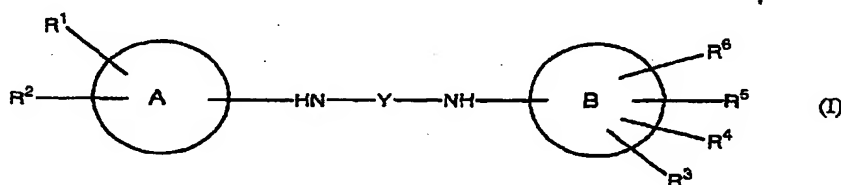
The objects on which the invention was based therefore consisted in providing novel compounds which are suitable for

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the treatment of diseases caused by protozoa, in particular for the treatment of malarial diseases.

Surprisingly, it has been found that asymmetric urea, guanidine, sulphamide, thiourea and oxalamide derivatives which are substituted by two aromatic hydrocarbon groups, of which one carries an amidine group that can optionally be substituted or cyclic and the other one a group capable of hydrogen bond formation, achieve this objective.

The present invention thus relates to a compound of the formula (I)



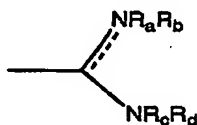
or a salt thereof, where

Y is C=O, C=S, C=NH, (C=O), or SO<sub>2</sub>;

(A) and (B) are independently an aromatic hydrocarbon group which optionally contains one or more heteroatoms selected from the group consisting of S, O and N, wherein the heteroatom N is optionally substituted with R', the heteroatom S is optionally bond to =O or (=O)<sub>2</sub>;

R' is hydrogen, hydroxyalkyl, haloalkyl, aminoalkyl, alkoxy, cyanoalkyl, alkyl or an unsaturated or saturated carbocyclic group selected from the group consisting of cyclopentyl, cyclohexyl, aryl and heteroaryl;

R<sup>1</sup> is



where  $R_a$  and  $R_c$  are independently hydrogen,  $-O-(CO)-R'$  (where  $R'$  is as defined above), hydroxy, hydroxyalkyl, haloalkyl, aminoalkyl, alkoxy, cyanoalkyl, alkyl or an unsaturated or saturated carbocyclic group selected from the group consisting of cyclopentyl, cyclohexyl, aryl, heteroaryl;  $R_b$  is an optional substituent which may be independent of  $R_a$  and  $R_c$  and may be selected from the group as defined above for  $R_a$  and  $R_c$ ;  $R_d$  is independently hydrogen or one of the following groups:

$-(CO)-R_e$  where  $R_e$  is independently hydrogen, alkoxy, alkylthio, halogen, haloalkyl, haloalkyloxy, hydroxyalkyl, hydroxyalkylamino, alkyl, aryl, heteroaryl, amino, aminoalkyl or alkylamino group;

$-(CH_2)_n-R_f$  where  $R_f$  is independently hydrogen, a hydroxyalkyl, an alkyl, an allyl, an amino, an alkylamino, a morpholino, 2-tetrahydrofuran, N-pyrrolidino, a 3-pyridyl, a phenyl, a benzyl, a biphenyl or another heterocyclic group and  $n$  is 0, 1, 2 or 3;

$-NR_gR_h$  where  $R_g$  and  $R_h$  are as defined above;

or  $R_i$  forms together with  $R_j$  a 5- or 6- membered unsaturated or saturated heterocyclic ring which optionally has 0 to 3 times substituents  $R''$ ;

the dotted line means a double bond unless there is a substituent  $R_k$  in the formula of  $R^1$  as defined above.

$R''$  is independently hydrogen, alkoxy, alkylthio, aminoalkyl, halogen,  $-CO_2R'$ ,  $-CR'O$ , haloalkyl, haloalkyloxy,  $-NO_2$ ,  $-CN$ , hydroxyalkyl, alkyl, aryl, heteroaryl, amino, alkylamino or aminoalkyl group or a double bonded oxygen, wherein  $R'$  is as defined above;

$R^1$  is a hydrogen, a halogen, alkoxy, alkylthio,  $-CO_2R'$ ,  $-CR'O$ , haloalkyl, haloalkyloxy,  $-NO_2$ ,  $-CN$ , hydroxy, hydroxyalkyl, alkyl, aryl, amino, alkylamino or aminoalkyl group;

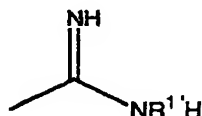
$R^2$  is a hydrogen, a halogen, haloalkyl,  $-NO_2$ ,  $-CN$ , alkyl or aryl group;

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- $R^1$  is a hydrogen or a group capable of hydrogen bond formation except for a group as defined for substituent  $R^1$ ;
- $R^5$  is hydrogen or, independently of  $R^4$ , a group selected from the groups as defined above for  $R^4$ ;
- $R^6$  is hydrogen or, independently of  $R^2$ , a group selected from the groups as defined above for  $R^2$ ; and

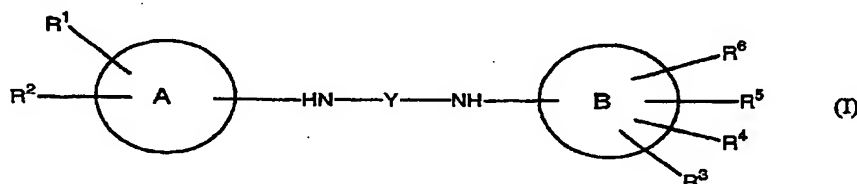
with the proviso that the compounds of the formula (I) are not compounds

in which Y is equal to C=O, both (A) and (B) are a phenyl group,  $R^1$  is the group



where  $R^1$  is hydrogen or phenyl,  $R^2$ ,  $R^3$ ,  $R^5$  and  $R^6$  are identical and are hydrogen,  $R^4$  is phenyl, benzyl, phenoxy, chloro or dimethylamino group in the 3- or 4-position to the NH-Y-NH group of the compound of the formula (I); or compounds in which (A) and (B) are phenyl and  $R^4$ ,  $R^5$  or  $R^6$  are in the ortho-position to the NH-Y-NH group of the compound of the formula (I).

In further embodiments, the invention relates to preparation processes, medicinal and veterinary uses and to pharmaceutical compositions or medicaments and in addition feed additives. In particular, the present invention furthermore relates to the use of a compound of formula (I)



or a salt thereof, where

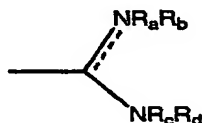


Y is C=O, C=S, C=NH, (C=O), or SO<sub>2</sub>;

(A) and (B) are independently an aromatic hydrocarbon group which optionally contains one or more heteroatoms selected from the group consisting of S, O and N, wherein the heteroatom N is optionally substituted with R', the heteroatom S is optionally bond to =O or (=O),;

R' is hydrogen, hydroxyalkyl, haloalkyl, aminoalkyl, alkoxy, cyanoalkyl, alkyl or an unsaturated or saturated carbocyclic group selected from the group consisting of cyclopentyl, cyclohexyl, aryl and heteroaryl;

R<sup>1</sup> is



where R<sub>a</sub> and R<sub>c</sub> are independently hydrogen, -O-(CO)-R' (where R' is as defined above), hydroxy, hydroxyalkyl, haloalkyl, aminoalkyl, alkoxy, cyanoalkyl, alkyl or an unsaturated or saturated carbocyclic group selected from the group consisting of cyclopentyl, cyclohexyl, aryl, heteroaryl; R<sub>b</sub> is an optional substituent which may be independently of R<sub>a</sub> and R<sub>c</sub> and may be selected from the group as defined above for R<sub>a</sub> and R<sub>c</sub>; R<sub>d</sub> is hydrogen or one of the following groups:

-(CO)-R<sub>e</sub> where R<sub>e</sub> is independently hydrogen, alkoxy, alkylthio, halogen, haloalkyl, haloalkyloxy, hydroxyalkyl, hydroxyalkylamino, alkyl, aryl, heteroaryl, amino, aminoalkyl or alkylamino group;

-(CH<sub>2</sub>)<sub>n</sub>-R<sub>e</sub> where R<sub>e</sub> is independently hydrogen, a hydroxy-alkyl, an alkyl, an allyl, an amino, an alkylamino, a morpholino, 2-tetrahydrofuran, N-pyrrolidino, a 3-pyridyl, a phenyl, a benzyl, a biphenyl or another heterocyclic group and n is 0, 1, 2 or 3;

-NR<sub>a</sub>R<sub>b</sub> where R<sub>a</sub> and R<sub>b</sub> are defined above;

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the dotted line means a double bond unless there is a substituent R<sub>n</sub> in the formula of R<sup>1</sup> as defined above.

R<sup>2</sup> is a hydrogen, a halogen, alkoxy, alkylthio, -CO<sub>2</sub>R', -CR'O, haloalkyl, haloalkyloxy, -NO<sub>2</sub>, -CN, hydroxy, hydroxyalkyl, alkyl, aryl, amino, alkylamino or aminoalkyl group;

R' is a hydrogen or a group capable of hydrogen bond formation except for a group as defined for substituent R<sup>1</sup>;

$R^6$  is hydrogen or, independently of  $R^2$ , a group selected from the groups as defined above for  $R^2$ ; and

for the preparation of a medicament for the treatment of diseases caused by protozoa.

Preferred embodiments of the invention are detailed in the dependent claims, the description and the examples.

Presently, "(A)" or "(B)" denotes the encircled A or B shown in the formula (I) or the formulae shown further below.

R is independently hydrogen, alkoxy, alkylthio,  $-CO_2R'$ ,  $-CR'O$ ,  $-NO_2$ ,  $-CN$ , halogen, haloalkyl, haloalkyloxy, hydroxyalkyl, hydroxyalkylamino, alkyl, aryl, heteroaryl, amino, aminoalkyl or alkylamino group.

An alkylthio group denotes an S-alkyl group, the alkyl group being as defined above.

An haloalkyl group denotes an alkyl group which is substituted by one to five preferably three halogen atoms, the alkyl group being as defined above.

A hydroxyalkyl group denotes an HO-alkyl group, the alkyl group being as defined as above;

An haloalkyloxy group denotes an alkoxy group which is substituted by one to five preferably three halogen atoms, the alkyl group being as defined above.

A hydroxyalkylamino group denotes an (HO-alkyl)-N- group or HO-alkyl-NH-, the alkyl group being as defined above.

An alkylamino group denotes an NH-alkyl or N-dialkyl group, the alkyl group being as defined above.

An aminoalkyl group denotes an NH<sub>2</sub>-alkyl, monoalkylaminoalkyl, dialkylaminoalkyl group, the alkyl group being as defined above.

A halogen group is chlorine, bromine, fluorine or iodine, fluorine being preferred.

An aryl group preferably denotes an aromatic group having 5 to 15 carbon atoms, in particular a phenyl group. This aryl group can optionally be substituted by one or more substituents R, where R is as defined above, preferably by haloalkyloxy or sulfonamide.

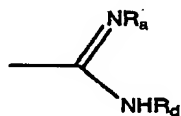
A heteroaryl group denotes a 5- or 6-membered heterocyclic group which at least contains one heteroatom like O, N, S. This heterocyclic group can be fused to another ring. For example, this group can be selected from an oxazol-2-yl, oxazol-4-yl, oxazol-5-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, isothiazol-3-yl, isothiazol-4-yl, isothiazol-5-yl, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 1,2,4-thiadiazol-3-yl, 1,2,4-thiadiazol-5-yl, 1,2,5-oxadiazol-3-yl, 1,2,5-oxa-diazol-4-yl, 1,2,5-thiadiazol-3-yl, 1-imidazolyl, 2-imidazolyl, 1,2,5-thiadiazol-4-yl, 4-imidazolyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 2-furanyl, 3-furanyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, 2-pyrazinyl, 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl, indolyl, indolinyl, benzo-[b]-furanyl, benzo[b]thiophenyl, benzimidazolyl, benzthiazolyl, quinazolinyl, quinoxazolinyl, or preferably isoxazol-3-yl, isoxazol-4-yl, isoxazol-5-yl, quinolinyl, tetrahydroquinolinyl, isoquinolinyl, tetrahydro-isoquinolinyl group. This heterocyclic group can optionally be substituted by one or more substituents R, where R is as defined above.

The compounds of the formula (I) according to the invention are disubstituted urea (Y is C=O), guanidine (Y is C=NH),

sulphamide (Y is  $\text{SO}_2$ ), thiourea (Y is  $\text{C}=\text{S}$ ) and oxalamide (Y is  $\text{C}=\text{O}$ ), derivatives. The compounds according to the invention are preferably the urea and thiourea derivatives, the urea derivatives being most preferred.

In a preferred embodiment of the invention, (A) is a phenyl group and (B) is an aromatic mono- or bicyclic hydrocarbon group having 5 to 15 carbon atoms, in particular having 5 to 10 carbon atoms, which optionally contains 1-4 N and/or O and/or S heteroatoms, in particular by 1 to 3 of these heteroatoms. Preferably, (A) is a phenyl and (B) is selected from a phenyl, furan, thiophene, oxazole, thiazole, isoxazole, isothiazole, 1,2,3-triazole, 1,3,4-thiadiazole, pyran, indole, isoindole, pyridine, pyridazine, pyrimidine, pyrazine, indazole, benzimidazole, triazine, indolizine, benzofuran, benzothiophene, benzothiophene-1,1-dioxide, benzothiazole, purine, quinolizine, quinoline, isoquinoline, cinnoline, phthalazine, quinazoline, naphthyridine and pteridine group. In this connection, any desired combination of these groups can be present for (A) and (B). Particularly preferred compounds are those in which at least (A) or at least (B) is a phenyl group, compounds in which (A) and (B) are each a phenyl group being most preferred.

Preferred compounds are those in which  $\text{R}^1$  is

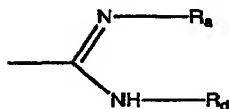


where  $\text{R}_a$  is hydrogen,  $-\text{O}-(\text{CO})-\text{R}'$  (where  $\text{R}'$  is as defined above), hydroxy and

$\text{R}_d$  is independently hydrogen,  $-\text{O}-(\text{CO})-\text{R}'$  (where  $\text{R}'$  is as defined above), hydroxy, biphenyl, alkylamino,  $-(\text{CH}_2)_n-\text{R}_2$  where  $\text{R}_2$  is an alkylamino, a saturated or unsaturated heterocyclic group and  $n$  is 0, 1 or 2;

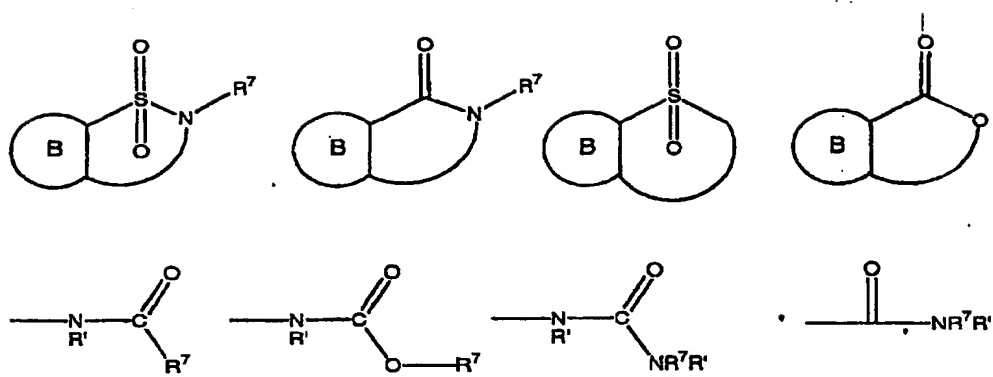
or where  $\text{R}_a$  and  $\text{R}_d$  form together a 5- or 6-membered saturated or unsaturated heterocyclic ring which is optionally substituted one or two times by a double bounded oxygen.

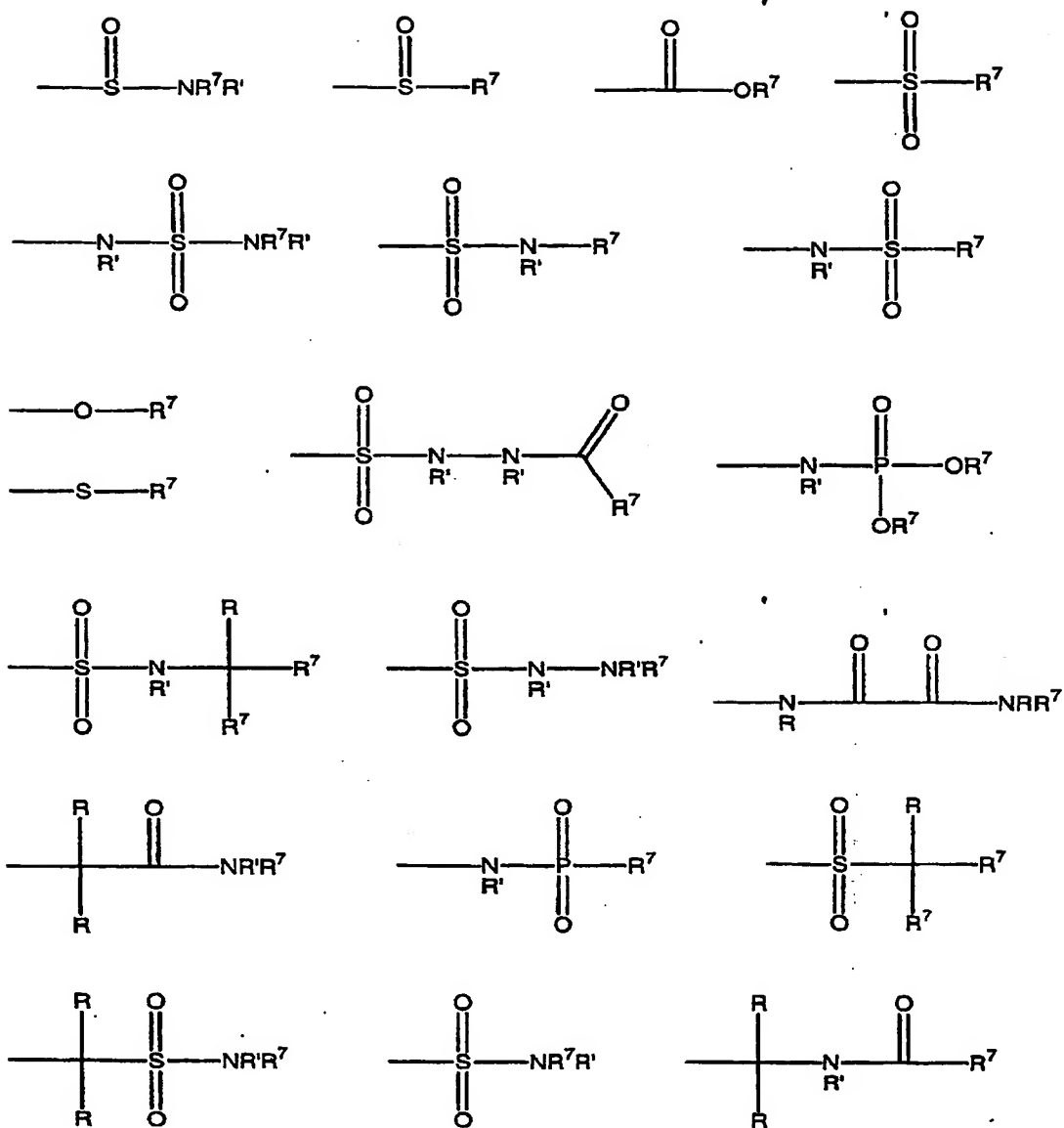
Most preferred compounds are those in which R<sup>1</sup> is



where  $R_1$  is hydrogen,  $-O-(CO)-R'$  (where  $R'$  is as defined above), hydroxy and  
 $R_2$  is hydrogen,  $-O-(CO)-R'$  (where  $R'$  is as defined above), hydroxy, 3-pyridyl, alkoxy,  $-CO_2R'$ , alkylamino,  $-(CH_2)_n-R_3$  where  $R_3$  is a saturated heterocyclic group  
or where  $R_1$  and  $R_2$  form a 5-membered heterocyclic ring which is optionally substituted one or two times by a double bounded oxygen.

The group R' is a group capable of hydrogen bond formation except for a group defined for substituent R'. A hydrogen bond is formed between a hydrogen atom covalently bond to an electronegative element (proton donor) and a lonely electron pair of an(other) electronegative atom (proton acceptor). R' can form the hydrogen bond by acting as proton donor or proton acceptor. Preferably, the groups capable of hydrogen bond formation are selected from a halogen, NO<sub>2</sub>, haloalkyl, haloalkyloxy or CN group or one of the groups mentioned below, where n is 0, 1, 2 or 3 and where R' in each case is independently hydrogen, alkyl, haloalkyl, adamantyl, hydroxyalkyl, hydroxyalkylamino, aminoalkyl, an aryl, biphenyl, or heteroaryl group, which is optionally substituted independently by one or more of the following groups: hydrogen, halogen, alkyl, haloalkyl, amino, aminoalkyl, nitro, alkylamino, hydroxyalkylamino, hydroxy, aryl, heteroaryl, alkoxy, haloalkoxy, COR', CONRR', SO<sub>2</sub>NRR', CO<sub>2</sub>R', where independently R and R' are as defined above. The group of R' is also selected from:





More preferably,  $\text{R}^1$  is selected from the groups





which optionally have 0 to 3 times substituents R'', where R'' is as defined above;  
 and a halogen, NO<sub>2</sub>, OCF<sub>3</sub>, CF<sub>3</sub>, sulfonamide, arylsulfonamide, biarylsulfonamide, amide, alkylsulfonamide, alkylsulfone, arylsulfone, alkylamide, arylamide, benzylamide, alkylthio, ester group where the aryl and benzyl substituents can again be substituted independently by one or more of the following groups: hydrogen, halogen, alkyl, haloalkyl, haloalkyloxy, aryl, amino, aminoalkyl, nitro, alkylamino, hydroxy, alkoxy, CONRR', hydroxyalkylsulfonamide, SO<sub>2</sub>NRR', CO<sub>2</sub>R', aminoalkylsulfonamide, (hydroxyalkyl)sulfonamide and (aminoalkyl)sulfonamide, wherein R and R' independently are as defined before.

Most preferably R<sup>4</sup> is a bisarylsulfonamide or a substituted benzylsulfonamide where the substituents are independently one or more of the following groups: hydrogen, halogen, haloalkyl, haloalkoxy, CONRR', SO<sub>2</sub>NRR' and CO<sub>2</sub>R', where R and R' independently are as defined above.

R<sup>1</sup>, R<sup>3</sup>, R<sup>5</sup> are preferably hydrogen.

R<sup>6</sup> is preferably hydrogen, a halogen, nitro, hydroxy, OCH<sub>3</sub>, CF<sub>3</sub>, or OCF<sub>3</sub> group.

The substituents R<sup>1</sup>, R<sup>4</sup> and/or R<sup>5</sup> in monocyclic groups of (A) and (B) are preferably present in the 3- or 4-position to the NH-Y-NH group of the compound of the formula (I). If (A) and/or (B) is a bicyclic group, R<sup>1</sup>, R<sup>4</sup> and/or R<sup>5</sup> are preferably present in the 1- to 4-position, in particular in the 3-position. The further substituents R<sup>2</sup>, R<sup>3</sup> and R<sup>6</sup> are preferably present in the 2- or 3-position, in each case relative to the NH-Y-NH group of the compound of formula (I). If (B) is a phenyl group R<sup>4</sup>, R<sup>5</sup> and/or R<sup>6</sup> is not in the 2- or 6-position to the NH-Y-NH-group of the compound of the formula (I).

Particularly preferred compounds of the formula (I) are the urea derivatives (i.e. Y is C=O), in which (A) and (B) in most

cases are a phenyl group but (B) also can be benzothiophene-1,1-dioxid,  $R^1$  is an optionally substituted or cyclic amidine group,  $R^4$  is a group capable of hydrogen bond formation, in particular a  $CF_3$ ,  $OCF_3$ , sulfonamide, benzylsulfonamide or arylsulfonamide, arylsulfone group, optionally substituted preferably by halogen,  $OCF_3$ , or sulfonamide and  $R^2$ ,  $R^3$ ,  $R^5$  and  $R^6$  are in each case hydrogen.

The salts of the compounds of formula (I) include phosphates, nitrates, hydrochlorides, hydrobromides, perchlorates, sulphates, citrates, lactates, tartrates, isethionates, maleates, fumarates, mandelates, benzoates, ascorbates, cinnamates, benzenesulfonates, methanesulfonates, stearates, succinates, glutamates, glycolates, toluene-4-sulfonates, formates, malonates, naphthalene-2-sulfonates, salicylates and acetates. These can be formed via well-known processes. Further suitable salts are all other salts customary in the pharmaceutical recipe, for example such as are described in *International Journal of Pharmaceutics*, 33 (1986), 201 - 217. The hydrochlorides are most preferred.

The compounds of the formula (I) according to the invention can be prepared according to the methods customary to the person skilled in the art or processes known from the literature. For example, these compounds can be prepared in liquid phase or via a solid-phase technique.

To prepare the urea derivatives, all methods known for the preparation of ureas can be employed. In the solid phase, for example, the methods which are described in *Organic Synthesis on Solid Phase*, Ed. F.Z. Dörwald, p. 331 ff, Wiley-VCH, Weinheim, 1999 can be applied. For the preparation of urea derivatives, suitable liquid-phase processes are described, for example, in Houben-Weyl, vol. E4, *Kohlensäure-Derivate* [Carboxylic acid derivatives] Publisher Hagemann, Georg Thieme Verlag, Stuttgart, 1983. Thus, in the liquid-phase technique a compound of the formula (I) in which  $R^4$  is a group capable of hydrogen bond formation and  $R^1$  is an amidine group can be prepared by reacting a suitable aniline which contains the group of  $R^4$  capable of hydrogen bond formation with a suitable

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isocyanate which contains a nitrile group or another group convertible to the amidine group, which can be present in protected or unprotected form. The nitrile group or the group convertible to the amidine group is then converted into the amidine group via known processes. Alternatively, the aniline containing the group capable of hydrogen bond formation can be converted into an isocyanate and this can be converted to an urea via known methods using a suitable aniline which contains a nitrile group or another group convertible into amidine, for this compare *The Chemistry of Amidines and Imidates*, Ed. Saul Patai, John Wiley & Sons, 1975. Furthermore, an amidine group protected by a protective group (suitable protective groups for this are described, for example, in *Nitrogen Protecting Groups: Recent Developments and New Applications*, G. Theodoridis, Tetrahedron 56 (2000), 2339-2358) can be converted into an isocyanate and reacted with an aniline containing the group capable of hydrogen bond formation. Compounds of this type lead, after the removal of the protective group, to the amidine-substituted urea. Anilines which contain an amidine or other basic functions can be converted directly into ureas according to processes known in the literature. In this connection, reagents can also be employed which include a latently activated carbonate unit which reacts with anilines under suitable conditions to give ureas. Examples of such reagents are carbonyldiimidazole or other reagents mentioned in *Advanced Organic Chemistry*, J. March, p. 396, John Wiley & Sons, New York, 1992. Processes suitable for the preparation of the urea derivatives are also described in DE-A-2 334 355, DE-A-2 928 485 and WO 9639382.

In a particularly preferred embodiment, the invention relates to a process for the preparation of the compounds according to the invention

wherein the process is characterized in that  
a compound of the formula (III)

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(V)

where

(B),  $R^3$ ,  $R^4$ ,  $R^5$  and  $R^6$  are as defined above.

All groups (A), (B), R<sup>1</sup>, R<sup>2</sup>, R<sup>4</sup>, R<sup>5</sup> and R<sup>6</sup> are defined in greater detail as described above under the compound of the formula (I) according to the invention.

For example, compounds of the formula (I) where R<sup>1</sup> is an amidine group can be prepared by the solid phase method. Therefore a suitable aromatic amidine is first linked to a polystyrene resin via a urethane function, for example by reaction of nitrobenzamidine in dimethylacetamide (DMA) in the presence of diisopropylethylamide (DIEA) with a nitrophenyl-carbonate Wang-resin ( D.M. Dixit, et al. (1978) Israel J. Chem., 17, 248; B.A. Dressman, et al. (1996) Tetrahedron Lett., 37, 937), for this also compare Solid Phase Synthesis of N-substituted amidinophenoxy pyridines as Factor X<sub>1</sub> Inhibitors, Raju Mohan et al., Bioorg. Med.'Chem. Lett. 8 (1998), 1877-1882.

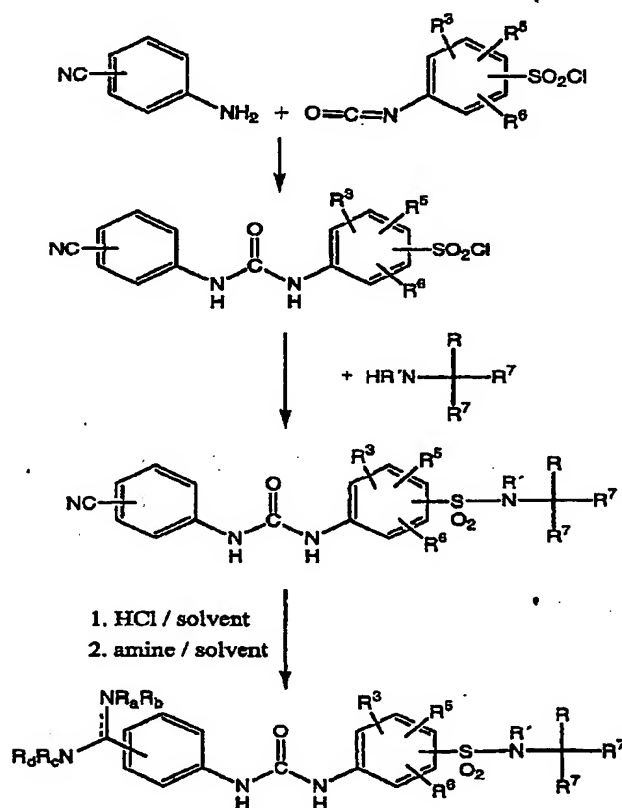
Afterwards, the nitro group is converted into an amino group by reduction using tin(II) chloride monohydrate, compare *Organic Synthesis on Solid Phase*, Ed. F.Z. Dörwald, p. 247, Wiley-VCH, Weinheim, 1999.

Conversion of the nitrile to the amidine is achieved by the Pinner-reaction. Substituted amidines are obtained by reacting the nitrile or iminoether with the appropriate amine according to Scheme 1 and mentioned in J. Med. Chem., 1996, 39, 4935-4941; Heterocycles, 1986, 24 (5), 1377- 1380; Bioorg. Med. Chem., 2001, 9, 585-592; Synthetic Commun., 1998, 28 (23),

4419-29; Eur. J. Org. Chem., 1998, 853-859 or J. Med. Chem., 1992, 35, 4393-4407.

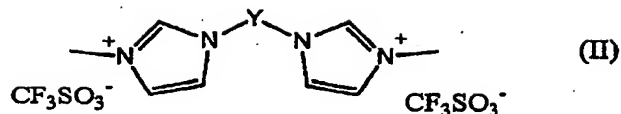
In case of acid labile groups present the nitrile is first converted to the amidoxime, which was reduced in the presence of zinc powder to the amidine after O-acylation with acetic acid anhydride as described in the European patent application EP 0990646.

Scheme 1:

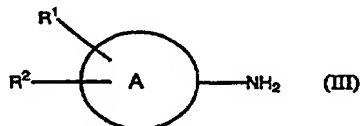


The invention also relates to a process for the preparation of compounds of the formula (I), in which Y is equal to  $\text{C=O}$ ,  $\text{C=S}$ ,  $\text{C=NH}$  or  $\text{SO}_2$ ,

where the process is characterized in that a compound of the formula (II)

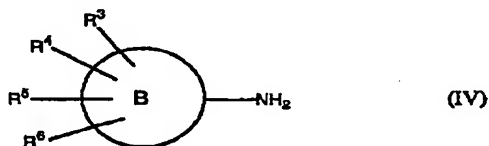


is reacted either with a compound of the formula (III)



where

(A), R<sup>1</sup> and R<sup>2</sup> are as defined above  
and with a compound of the formula (IV)



where

(B), R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup> and R<sup>6</sup> are as defined above.

The reagent 1,1'-carbonylbis(3-methylimidazolium) triflate (CBMIT; the triflate radical designates the trifluoromethanesulfonyl radical) is used, which is described in 1,1'-carbonylbis(3-methylimidazolium) triflate: An efficient Reagent for Aminoacylations, A. K. Saha et al., J. Am. Chem. Soc. **1989**, 111, 4856 - 4859)

This reagent enables, under mild conditions, the preparation of compounds of the formula (I), in which Y is equal to C=O, C=S, C=NH or SO<sub>2</sub>. The reaction with this reagent can be carried out either in the liquid phase or on solid phase, the preparation in the liquid phase being preferred. All groups (A), (B), R<sup>1</sup>, R<sup>2</sup>, R<sup>4</sup>, R<sup>5</sup> and R<sup>6</sup> are defined in greater detail as described above under the compound of the formula (I) according to the invention.

In literature, CBMIT has been used to make amides (Ashis K. Saha, et al. JACS 1998, 11, 4856-4859) and asymmetric ureas (Robert A. Batey, Tetrahedron Letters 39 (1998) 6267-6270).

Thiourea derivatives can also be made by other methods as conversion of ureas to thioureas by Lawesson reagent or  $P_2S_5$  (Bull. Soc. Chim., Belg. Synth. 1978, 87, 229-238 or Org. Synth., 1984, 62, 158-164 or Chem. Rev., 1961, 61, 45-86.) Other methods to make thioureas are described in J. Comb. Chem., 2000, 2, 75-79 or in Houben-Weyl, Vol. E4, Kohlensäure-Derivate [Carbonic acid derivatives], Editor Hagemann, Georg Thieme Verlag, Stuttgart, 1983, 484-505.

Bisarylsulphamides can also be prepared by other methods as described in Tetrahedron Letters, 1997, Vol. 38, 8691-8694 or in WO 01/36383.

Bisaryloxalamides can also be prepared by using oxalic acid ester (preferably hexafluoroisopropylester) or oxalylchloride instead of CBMIT. These methods are described in J. Org. Chem., 1997, 62, 5908-5919 or in US 3529982, US 4003875, and in EP 0507732.

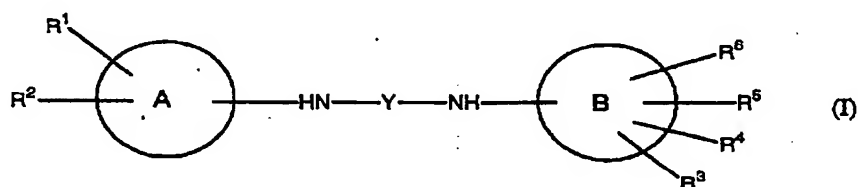
The compounds according to the invention and medicaments prepared therewith are generally suitable for the treatment of diseases which occur due to attack of humans or animals by protozoa. Veterinary- and human-pathogenic protozoa of this type are preferably parasites of the phyla Apicomplexa and Sarcomastigophora, in particular trypanosomes, plasmodia (malarial parasites), toxoplasma, leishmania, babesia and theileria, cryptosporidiidae, sarcocystidae, eimeria and isospora, amoebae and trichomonads. The compounds or corresponding medicaments are particularly preferably suitable for the treatment of diseases caused by plasmodia, in particular for the treatment of tropical malaria, which is caused by *Plasmodium falciparum*, for the treatment of benign tertian malaria, caused by *Plasmodium vivax* and *Plasmodium ovale* and for the treatment of quartan malaria, caused by *Plasmodium malariae*; they are moreover suitable for the treatment of toxoplasmosis, caused by *Toxoplasma gondii*, of

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coccidiosis, caused by *Isospora belli*, of intestinal sarcosporidiosis, caused by *Sarcocystis suihominis*, of cryptosporidiosis, caused by *Cryptosporidium parvum*, of the African sleeping sickness caused by *Trypanosoma brucei rhodesiense* and *Trypanosoma brucei gambiense*, of Chagas' disease, which is caused by *Trypanosoma cruzi*, the cutaneous and visceral and also other forms of leishmaniosis caused by various leishmania species, and also for the treatment of animals which have been infected by veterinary pathogenic protozoa, such as by *Theileria parva*, the parasite of east-coast fever of cattle, *Trypanosoma congolense congolense*, *Trypanosoma vivax vivax* and *Trypanosoma brucei brucei*, parasites causing Nagana cattle disease, *Babesia begemina*, the parasite of Texas fever in cattle and buffalo, *Babesia bovis*, the parasite of european bovine babesiosis, and babesioses in dogs, cats and sheep, sarcocystidae, the parasites of sarcocystosis in sheep, cattle and pigs, cryptosporidiidae, the parasites of cryptosporidiosis in cattle and birds, coccidia, the parasites of coccidiosis of rabbits, cattle, sheep, goats and pigs, but in particular of chicken and turkey hens as for example *Eimeria tenella*. Most preferred is the use of the compounds according to the invention for the treatment of coccidiosis or malarial diseases or for the production of a medicament or, if appropriate, of a feed for the treatment of coccidiosis or malarial diseases. The treatment can in this case be carried out prophylactically or curatively.

The present invention also relates to the use of a compound of the formula (I)



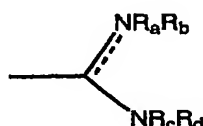
or a salt thereof, where

Y is C=O, C=S, C=NH, (C=O), or SO<sub>2</sub>;

(A) and (B) are independently an aromatic hydrocarbon group which optionally contains one or more heteroatoms selected from the group consisting of S, O and N, wherein the heteroatom N is optionally substituted with R', the heteroatom S is optionally bond to =O or (=O),;

R' is hydrogen, hydroxyalkyl, haloalkyl, aminoalkyl, alkoxy, cyanoalkyl, alkyl or an unsaturated or saturated carbocyclic group selected from the group consisting of cyclopentyl, cyclohexyl, aryl and heteroaryl;

R<sup>1</sup> is



where R<sub>a</sub> and R<sub>b</sub> are independently hydrogen, -O-(CO)-R' (where R' is as defined above), hydroxy, hydroxyalkyl, haloalkyl, aminoalkyl, alkoxy, cyanoalkyl, alkyl or an unsaturated or saturated carbocyclic group selected from the group consisting of cyclopentyl, cyclohexyl, aryl, heteroaryl; R<sub>c</sub> is an optional substituent which may be independently of R<sub>a</sub> and R<sub>b</sub> and may be selected from the group as defined above for R<sub>a</sub> and R<sub>b</sub>; R<sub>d</sub> is hydrogen or one of the following groups:

-(CO)-R<sub>e</sub> where R<sub>e</sub> is independently hydrogen, alkoxy, alkylthio, halogen, haloalkyl, haloalkyloxy, hydroxyalkyl, hydroxyalkylamino, alkyl, aryl, heteroaryl, amino, aminoalkyl or alkylamino group;

-(CH<sub>2</sub>)<sub>n</sub>-R<sub>f</sub> where R<sub>f</sub> is independently hydrogen, a hydroxy-alkyl, an alkyl, an allyl, an amino, an alkylamino, a morpholino, 2-tetrahydrofuran, N-pyrrolidino, a 3-pyridyl, a phenyl, a benzyl, a biphenyl or another heterocyclic group and n is 0, 1, 2 or 3;

-NR<sub>g</sub>R<sub>h</sub> where R<sub>g</sub> and R<sub>h</sub> are defined above;

or R<sub>d</sub> forms together with R<sub>c</sub> a 5- or 6- membered unsaturated or saturated heterocyclic ring which optionally has 0 to 3 times substituents R'';

the dotted line means a double bond unless there is a substituent  $R_2$  in the formula of  $R^1$  as defined above.

$R''$  is independently hydrogen, alkoxy, alkylthio, aminoalkyl halogen,  $-\text{CO}_2R'$ ,  $-\text{CR}'\text{O}$ , haloalkyl, haloalkyloxy,  $-\text{NO}_2$ ,  $-\text{CN}$ , hydroxyalkyl, alkyl, aryl, heteroaryl, amino, alkylamino or aminoalkyl group or a double bounded oxygen, wherein  $R'$  is as defined above;

$R^2$  is a hydrogen, a halogen, alkoxy, alkylthio,  $-\text{CO}_2R'$ ,  $-\text{CR}'\text{O}$ , haloalkyl, haloalkyloxy,  $-\text{NO}_2$ ,  $-\text{CN}$ , hydroxy, hydroxyalkyl, alkyl, aryl, amino, alkylamino or aminoalkyl group;

$R^3$  is a hydrogen, a halogen, haloalkyl,  $-\text{NO}_2$ ,  $-\text{CN}$ , alkyl or aryl group;

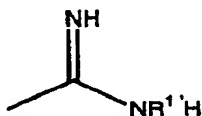
$R^4$  is a hydrogen or a group capable of hydrogen bond formation except for a group as defined for substituent  $R^1$ ;

$R^5$  is hydrogen or, independently of  $R^4$ , a group selected from the groups as defined above for  $R^4$ ;

$R^6$  is hydrogen or, independently of  $R^3$ , a group selected from the groups as defined above for  $R^3$ ; and

with the proviso that the compounds of the formula (I) are not compounds

in which Y is equal to  $\text{C}=\text{O}$ , both (A) and (B) are a phenyl group,  $R^1$  is the group



where  $R''$  is hydrogen or phenyl,  $R^2$ ,  $R^3$ ,  $R^4$  and  $R^6$  are identical and are hydrogen,  $R^5$  is phenyl, benzyl, phenoxy, chloro or

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dimethylamino group in the 3- or 4-position to the NH-Y-NH group of the compound of the formula(I); or compounds in which (A) and (B) are phenyl and R<sup>4</sup>, R<sup>5</sup> or R<sup>6</sup> are in the ortho-position to the NH-Y-NH group of the compound of the formula(I).

The compounds used according to the invention can be administered orally or parenterally (e.g. intravenously, intraperitoneally or intramuscularly), oral administration being preferred. In this case, the compounds are used alone as monosubstances or in combination with other active compounds, for example with medicaments already known for the treatment of diseases caused by protozoa, where in the latter case a favourable, additively reinforcing action can be observed. Amounts suitable for administration are 1 to 1000 mg/day in humans or animals. The present invention therefore also relates to a pharmaceutical composition which contains at least the compound according to the invention. In addition, the pharmaceutical composition can contain further customary, as a rule inert, vehicles or excipients.

The invention moreover relates to a feed additive which contains at least the compound according to the invention. Customary feed mixtures, for example, in particular those for poultry or agricultural animals, can be admixed to this feed additive. When used as a feed additive, the amount of the compound according to the invention is 20 to 750 ppm, preferably 2 to 200 mg.

The compounds used according to the invention can also be employed in the form of a precursor (prodrug) or in appropriately modified form which releases the active compound in vivo or under physiological conditions. Precursors of this type can be obtained, for example, by masking the amidine group by a hydroxy or -O-(CO)-R' group, wherein R' is as defined above (e.g. according to WO 95/01168) or by any other method as described in the literature, e.g. J. Med. Chem. 43, No. 19, p. 3461 (2000).

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The invention thus makes available novel medicaments for the treatment of the various forms of malaria, in particular for the treatment of tropical malaria. It was surprising that the compounds proved active not only against chloroquine-sensitive, but also against chloroquine-resistant, *Plasmodium falciparum* strains. In addition to the hitherto customary treatment of the later erythrocytic stage of the malarial parasite, with these compounds the treatment of the early form of malaria by destruction of the parasites even in the liver also appears to be very particularly advantageous with these compounds.

The invention is illustrated in greater detail with the aid of the following examples, which are preferred embodiments of the invention and do not restrict the scope of the invention.

#### **EXAMPLES**

##### **Abbreviations index**

The following abbreviations are presently used:

DMA = dimethylacetamide; DCM = dichloromethane; DMF = dimethylformamide; DIEA = diisopropylethylamide; TFA = trifluoroacetic acid; CBMIT = 1,1'-carbonylbis(3-methylimidazolium) triflate; eq = equivalents; rt = room temperature; h = hours; HPLC-MS = high-performance liquid chromatography-mass spectrometry.

##### **Reagents used**

Wang-resin (200-400 mesh) with a functional loading of 1.1 mmol/g was obtained from Calbiochem-Novabiochem, Postfach 1167, D-65796 Bad Soden.

##### **Preparation process**

The compounds described in the following table were prepared according to one or more of the following synthesis methods 1

to 9. The compounds prepared were then investigated for their antimalarial activity.

#### Analytical & termination

In the following the mass found by mass spectrometry, the exact molecular mass, the NMR-data at 300 MHz (abbreviations: br. = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, J =  $^1\text{H}$ - $^1\text{H}$  coupling constant).

#### Synthesis method 1:

Wang-resin was suspended in dry DMA, p-nitrophenyl-chloroformate (1.2 eq) and DIEA (1.2 eq) were added and the mixture was kept on a shaker for 12 h. The resin was collected by filtration and washed several times with isopropanol and DCM. The resin was then suspended again in DMA and 3-nitro-phenylbenzamidine (1.5 eq) and DIEA (1.5 eq) were added and the mixture was kept on a shaker overnight and then washed with isopropanol and DCM. A solution of  $\text{SnCl}_4 \cdot \text{H}_2\text{O}$  (1M) in DCM/DMF (1/1) was then added and the mixture was shaken for a further 5 h.

Finally, the resin was washed again with isopropanol and DCM and then dried. This resin was then used for the synthesis methods 2, 2a, 2b, 3, 5 and 6.

#### Synthesis method 2:

An aliquot (100 mg) of the resin modified according to synthesis method 1 was suspended in dry DCM and 5 eq of the appropriate isocyanate were added. The mixture was kept in a suitable vessel overnight on a shaker. The resin was collected by filtration and washed successively with DCM, isopropanol and DCM. The resin was then treated with 50% strength TFA in DCM for 1 h, filtered and the filtrate was concentrated in vacuo. The crude urea was first analysed by HPLC-MS and then purified by preparative HPLC.

#### Synthesis method 2a:

An aliquot (100 mg) of the resin modified according to synthesis method 1 was suspended in dry DCM and 5 eq

nitrophenylisocyanate were added. The mixture was kept in a suitable vessel overnight on a shaker. The resin was collected by filtration and washed successively with DCM, isopropanol and DCM.

A solution of  $\text{SnCl}_4 \cdot \text{H}_2\text{O}$  (1 M) in DCM/DMF (1/1) was then added and the mixture was shaken for a further 5 h. Finally, the resin was washed again with isopropanol and DCM and then dried. The so obtained resin was treated with DIEA (2 eq) and the appropriate acid chloride (2 eq). The resin was collected by filtration and washed successively with DCM, isopropanol and DCM. The resin was then treated with 50% strength TFA in DCM for 1 h, filtered and the filtrate was concentrated in vacuo. The crude urea was first analysed by HPLC-MS and then purified by preparative HPLC.

#### Synthesis method 3:

The modified resin prepared according to synthesis method 1 was reacted overnight at rt in dry DCM with chlorosulfonyl-isocyanate (1.5 eq). The resin was collected by filtration, washed with DCM and dried.

A small aliquot of the resin (100 mg) was reacted at 80°C for 3 h with the appropriate amine and DIEA in DMA. The resin was collected by filtration, washed with isopropanol and DCM and then treated with 50% strength TFA for 1 h. The TFA solution was collected by filtration, concentrated in vacuo and analysed by analytical HPLC-MS. The crude product was purified by preparative HPLC.

#### Synthesis method 4:

1,1-carbonyldiimidazole (1 eq) was dissolved in 5 ml nitromethane. The solution was cooled to 4 °C and methyltriflate (2 eq) were added dropwise. The reaction was stirred for 30 min at 4 °C, then the appropriate aniline or sulfonamide dissolved in 2 ml DMA was added dropwise. The reaction was stirred for 2.5 h at rt, then aminobenzamidine dihydrochloride dissolved in 1 ml DMA containing DIEA (1 eq) was added. After stirring overnight at rt the solvent was evaporated and the product purified by flash chromatography on

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silica gel using a gradient of AcOEt-MeOH from 5% to 55% MeOH or by preparative HPLC.

**Synthesis method 4a:**

Analog to method 4 only that 1,1-thiocarbonyldiimidazole (1 eq) was used instead of 1,1-carbonyldiimidazole.

**Synthesis method 4b:**

Analog to method 4 only that 1,1-sulfonyldiimidazole (1 eq) was used instead of 1,1-carbonyldiimidazole.

**Synthesis method 5:**

An aliquot (100 mg) of the modified resin prepared according to synthesis method 1 was treated for 1-2 h with CBMIT reagent (5 eq) in dry nitromethane. The resin was collected by filtration and the appropriate aniline (5 eq) in DMA were added and the mixture was kept for 12 h in a suitable vessel on a shaker. The resin was collected by filtration, washed with isopropanol and DCM and treated for 1 h with 50% strength TFA in DCM. The TFA solution was concentrated in vacuo and the crude urea derivative was analysed by analytical HPLC-MS. The crude urea derivative was then purified by preparative HPLC.

**Synthesis method 6:**

A first aniline derivative (0.1 mmol) was dissolved (or suspended) in dry nitromethane (0.4-1.0 ml) and CBMIT (0.5 ml/ 0.1 mmol) was added at 0 °C and the mixture was stirred for 1 h. The modified resin (100 mg/ 0.1 mmol) prepared according to synthesis method 1 were added to this reaction mixture and it was kept for 12 h in a suitable vessel on a shaker. The resin was collected by filtration, washed and treated for 1 h with 50% strength TFA. The TFA solution was collected by filtration and concentrated in vacuo. The crude urea derivative was analysed by analytical HPLC-MS and purified by preparative HPLC.

**Synthesis method 7:**

To a solution of the of hexafluoroisopropyl oxalate in dry DCM or DMF the amine (1.0 eq.) was added. After 24 h at rt the second amine (1.0 eq.) was added. After 2 d at rt the

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precipitate was filtered. The solvent of the filtrate was removed in vacuo and the product crystallized from methanol or purified by flash chromatography.

**Synthesis of N-(4-benzylsulfamoylphenyl)-N'-(3-carbamimidoylphenyl)-oxalamide**

To a solution of hexafluoroisopropyl oxalate (500 mg, 1.28 mmol) in DCM (5 ml) 3-aminobenzonitrile (1.0 eq. 151 mg) was added. After 24 h at rt the 4-Amino-N-benzylbenzenesulfonamide (363 mg/ 1.28 mmol) and N,N-dimethylacetamide (5 ml) were added. After 30 h at rt, 6 h at 40 °C and 20 h at rt the precipitate was filtered. The solvent of the filtrate was removed in vacuo and the nitrile crystallized from MeOH.

To the nitrile (50 mg, 115 µmol) a solution of HCl in MeOH (25 ml) and DCM (30 ml) were added at 0 °C. After 20 h at rt the solvent was removed and the iminoether dried in vacuo. The iminoether was dissolved in a solution of NH<sub>3</sub> in MeOH (4 ml, 7 M) and toluene (3 ml). After 2 h at 60 °C the solvent was removed in vacuo. After dilution in chloroform and MeOH (5 ml each) solid byproducts were removed by filtration. After removal of the solvent purification by flash chromatography (A: AcOEt, B: MeOH, 100→35% A within 25 min) yielded the amidine (50 %). <sup>1</sup>H-NMR (d<sub>4</sub>-MeOH): 4.07 (s, 2 H, CH<sub>2</sub>-Ph), 7.18-7.25 (m, 5 H, Ph), 7.59 (dt, J = 7.8 and 1.7 Hz, 1 H, 4-H), 7.64 (t, J = 7.8 Hz, 1 H, 5-H), 7.83 (dt, J = 9.0 and 2.1 Hz, 2 H, 3',5'-H), 7.96 (dt, J = 9.0 and 2.1 Hz, 2 H, 2',6'-H), 7.69 (dt, J = 7.6 and 1.7 Hz, 1 H, 6-H), 8.13 (t, J = 1.7 Hz, 1 H, 2-H). <sup>13</sup>C-NMR (d<sub>4</sub>-MeOH): 47.9 (CH<sub>2</sub>-Ph), 120.7 (C-2), 121.5 (C-2',6'), 125.3 (C-4), 126.9 (C-6), 128.5 (C-4''), 128.9, 129.1 and 129.4 (C-3',5',2'',3''), 131.2 (C-5), 130.6, 138.2, 138.6, 139.7 and 142.3 (C-1,3,1',3',1''), 159.7 and 159.9 (C=O), 168.6 (C=NH).

**Synthesis of N-(3-benzylsulfamoylphenyl)-N'-(3-carbamimidoylphenyl)-oxalamide**

The compound was synthesized in the same manner as the 4-benzylsulfamoylphenyl analogue, with the exception that the nitrile was purified by chromatography (with a PE/AcOEt-gradient). The amidine was obtained as a mixture of the free

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amidine and the acetate.  $^1\text{H-NMR}$  ( $d_6$ -DMSO): 4.02 (s, 2 H,  $\text{CH}_2$ -Ph), 7.18-7.30 (m, 5 H), 7.54-7.66 (m, 4 H), 8.07-8.05 (m, 1 H) and 8.17 (dt,  $J = 7.1$  and  $2.0$  Hz, 1 H) (aromatic-H), 8.29-8.31 (m, 1 H) and 8.44-8.46 (m, 1 H) (H-1 and H-1').  $^{13}\text{C-NMR}$  ( $d_6$ -DMSO): 46.1 ( $\text{CH}_2$ -Ph), 118.5 and 119.9 (C-1 and C-1'), 122.4, 124.0, 124.2, 125.2, 127.0, 127.5, 128.1, 129.0, 129.5, 129.6, 137.6, 138.0, 138.0 ( $\text{C}_{\text{ar}}$ ), 158.6 and 158.6 ( $\text{O}=\text{C}-\text{N}$ ), 166.1 ( $\text{N}=\text{C}-\text{N}$ ).

#### Synthesis method 8:

The nitrobenzenesulfonylchloride or nitrobenzoylchloride derivate (1 eq.) was added to a solution of benzylamine or its hydrochloride (1 - 2 eq) and triethylamine or DIEA (1 - 2 eq.) in dry THF or acetonitrile at 0 °C under inert atmosphere. The reaction mixture was warmed to ambient temperature after 10 min and stirred for a further 18 to 72 h. It was then concentrated in vacuo, water was added and the resulting precipitate was filtered and dried in vacuo. The residue was dissolved in methanol, ethanol or ethanol / ethyl acetate (1/2) and hydrogenated for 18 h over palladium on charcoal. The mixture was filtered and the filtrate concentrated in vacuo. The residue (1 eq.) was dissolved in anhydrous solvent (DCM, DCM/DMA, THF or THF/DMA) under inert atmosphere, the cyanophenylisocyanate (1 eq.) was added and the mixture was stirred at 20 - 67 °C for 18 h. The precipitate was filtered and dried in vacuo. If no precipitate formed, the solution was concentrated and the residue crystallized with an appropriate solvent. The urea derivatives thus obtained were recrystallized from ethanol/water if necessary and again dried in vacuo. An aliquot of the substance was dissolved in anhydrous hydrochloric acid solution in methanol at 0 °C and stirred for 18 h, during which the mixture was warmed to ambient temperature. The resulting precipitate was filtered and dried in vacuo. If no precipitate formed, the solution was concentrated and dried in vacuo. In case an unsubstituted amidine was to be synthesized, the residue was dissolved in 7 M methanolic ammonia solution and refluxed for 2 h. If an alkylated amidine or an amidoxime was to be synthesized, the residue was dissolved in methanol or ethanol and triethylamine (0 - 10 eq.) and the amine or its hydrochloride or

hydroxyamine hydrochloride (1 - 6 g.) was added and the mixture was refluxed for 18 h. The precipitate was filtered and dried in vacuo. If no precipitate formed, the solution was concentrated in vacuo and purified by column chromatography (silica gel column, ethyl acetate / methanol) or preparative HPLC. For the synthesis of an acylated amidine, the acid chloride (2.5 eq.) was added to the solution of the amidine (1 eq.) and triethylamine (5 eq.) in anhydrous DMA, at 0 °C. After 10 min, the mixture was warmed to room temperature and stirred for another 2 h. The precipitate was separated by centrifugation, washed with ethyl acetate / diethylether and dried in vacuo.

**Synthesis of 4-[3-(3-carbamimidoylphenyl)-ureido]-N-(4-sulfamoylbenzyl)-benzamide:**

A solution of 4-nitrobenzoylchloride (1.85 g, 1 eq.) in acetonitrile (20 ml) was added to a solution of 4-aminomethyl-benzenesulfonamide hydrochloride (4.44 g, 2 eq.) and triethylamine (2.78 ml, 2 eq.) in acetonitrile (40 ml) at 0 °C under inert atmosphere. After the addition was completed, the mixture was warmed to rt and stirred for 3 d. Water was added and the mixture was concentrated under reduced pressure. The resulting precipitate was filtered off and washed with water and methanol to yield 2.86 g (85 %) of 4-nitro-N-(4-sulfamoylbenzyl)-benzamide.

4-Nitro-N-(4-sulfamoylbenzyl)-benzamide (2.86 g) was dissolved in methanol (500 ml), palladium on charcoal (1 g, 5 %) was added and the mixture hydrogenated overnight. The catalyst was removed by filtration and the filtrate concentrated in vacuo. Yield: 2.13 g (89 %) of 4-amino-N-(4-sulfamoylbenzyl)-benzamide.

4-Amino-N-(4-sulfamoylbenzyl)-benzamide (2.13 g, 1 eq.) was dissolved anhydrous in DMA (10 ml) under inert atmosphere, anhydrous DCM (30 ml) was added and the solution was cooled to 0 °C. A solution of 3-cyanophenylisocyanate (1.9 g, 1.9 eq.) in anhydrous DCM (10 ml) was added and the mixture stirred over night. The resulting precipitate was filtered off, washed

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with methanol and dried in vacuo to yield 2.38 g (76 %) 4-[3-(3-cyanophenyl)-ureido]-N-(4-sulfamoylbenzyl)-benzamide.

4-[3-(3-Cyanophenyl)ureido]-N-(4-sulfamoylbenzyl)-benzamide (449 mg) was suspended in methanolic hydrochloride acid solution (50 ml) at 0 °C under inert atmosphere and stirred for 20 h during which the mixture was warmed to rt. The precipitate was filtered off, washed with methanol and dried in vacuo. Yield: 0.37 g (77 %) of 3-{3-[4-(4-sulfamoylbenzylcarbamoyl)phenyl]ureido}-benzimidic acid methyl ester

3-{3-[4-(4-Sulfamoylbenzylcarbamoyl)-phenyl]-ureido}-benzimidic acid methyl ester (370 mg) was dissolved in methanolic ammonia solution (5 ml, 7 M) and refluxed for 4 h. The mixture was filtered, the filtrate concentrated in vacuo and diethylether was added. The resulting precipitate (300 mg) was filtered off. 100 mg were suspended in ethyl acetate/methanol/ammonia, filtered off, washed with ethyl acetate and ether and dried in vacuo to yield 60 mg of 4-[3-(3-carbamimidoylphenyl)-ureido]-N-(4-sulfamoylbenzyl)-benzamide. Analytical data see table 1.

**Synthesis of 3-{3-[4-(4-nitrobenzenesulfonyl)-phenyl]-ureido}-benzamidine:**

A solution of 3-cyanophenylisocyanate (1 g, 1 eq.) in anhydrous DCM (10 ml) was added to a solution of 4-(4-nitrophenylsulfonyl)aniline (2 g, 1 eq.) in anhydrous DCM (40 ml) under inert atmosphere. The mixture was stirred at rt for 1 d, then refluxed for 1 d. The precipitate was filtered off, refluxed in ethanol for 2 h, filtered off again and dried in vacuo. Yield: 1.65 g (54 %) of 1-(3-cyanophenyl)-3-[4-(4-nitrobenzenesulfonyl)-phenyl]-urea.

1-(3-Cyanophenyl)-3-[4-(4-nitrobenzenesulfonyl)-phenyl]-urea (500 mg) was suspended in methanolic hydrochloride acid solution (150 ml) at 0 °C under inert atmosphere and stirred for 2 d during which the mixture was warmed to rt. The precipitate was filtered off and dried in vacuo to give 3-{3-

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[4-(4-nitrobenzenesulfonyl)-phenyl]-ureido}-benzimidic acid methyl ester.

This was suspended in methanolic ammonia solution (4 ml, 7 M), the mixture was refluxed for 2 h and cooled to rt. The precipitate was filtered off and dried in vacuo to yield 132 mg (26 % over 2 steps) of 3-{3-[4-(4-nitrobenzenesulfonyl)-phenyl]-ureido}-benzamidine.

**Synthesis of 4-{3-[4-(4-nitrobenzenesulfonyl)-phenyl]-ureido}-N-pyridine-3-yl-benzamidine**

3-{3-[4-(4-Nitrobenzenesulfonyl)-phenyl]-ureido}-benzimidic acid methyl ester (50 mg, 1 eq) was suspended in methanol (10 ml) and 3-aminopyridine (12 mg, 1.2 eq) was added. The solution was stirred for 72 h at 70 °C. The precipitate was filtered off and dried in vacuo.

**Synthesis of 4-[3-(4-benzylsulfamoylphenyl)-ureido]-benzamidine:**

A solution of p-Nitrobenzenesulfonylchloride (274 g, 1.2 eq) in DCM (1 l), was added to a solution of benzylamine (500 g, 1 eq) and triethylamine (469 ml, 1.5 eq) in DCM (1 l) at 4 °C in small portions and then stirred for 1 h. Afterwards the mixture was stirred at rt for 16 h. The solvent was removed in vacuo and the residue was washed with a mixture of DCM/PE (1/1) at 4 °C, filtered and dried in vacuo to give N-Benzyl-4-nitrobenzenesulfonamide. Yield 90 %.

N-benzyl-4-nitrobenzenesulfonamid (60 g, 1 eq) was dissolved in anhydrous ethanol (2 l) and Pd/C (10 g, 1 eq) was added under inert atmosphere. The mixture was stirred under a hydrogen atmosphere for 8 h. Then the solution was filtered over Celite, concentrated in vacuo to ~ 40 ml and then crystallized. The product was washed twice with ethanol (20 ml) at 4 °C, filtered and dried in vacuo to give 4-amino-N-benzylbenzenesulfonamide. Yield 75 %.

A solution of 3-cyanophenylisocyanate (6.4 g, 1 eq) in DCM (100 ml), was added to 4-amino-N-benzylbenzenesulfonamide (10.4 g, 1 eq), dissolved in DCM (100 ml), at 4 °C in small portions, stirred for 1 h. Afterwards the mixture was stirred

at rt for 16 h. The solvent was removed in vacuo and the residue was recrystallized from ethanol/water (1/1). The product was filtered, washed 2 times with ethanol/water (1/1) at 4 °C, and dried in vacuo to give N-benzyl-4-[3-(3-cyanophenyl)-ureido]-benzenesulfonamide. Yield 90 %.

N-benzyl-4-[3-(3-cyanophenyl)-ureido]-benzenesulfonamide (22 g, 1 eq) was dissolved in ethanol (150 ml). Hydrochloric acid was bubbled through the solution for 2 h at 4 °C. Then the solution was stirred for 1 h at rt. The solvent was removed in vacuo. The product was washed with ethanol/water (1/1) at 4 °C, and dried in vacuo to give 3-[3-(4-benzylsulfamoylphenyl)-ureido]-benzimidic acid ethyl ester. Yield 75 %.

3-[3-(4-benzylsulfamoylphenyl)-ureido]-benzimidic acid ethyl ester (21 g, 1 eq) was dissolved in ethanol (150 ml).  $\text{NH}_3$  was bubbled through the solution for 3 h. Then the solution was stirred for 2 h at rt. The solvent was removed in vacuo and the residue recrystallized from ethanol/water (1/1). The pure product was dissolved at 80 °C in ethanol (200 ml) and etheric hydrochloridic acid (200 ml, 1 M) was added. The mixture was filled up to a volume of 1 l with ether, the resulting precipitate was filtered and dried in vacuo to give over 3-[3-(4-Benzylsulfamoyl-phenyl)-ureido]-benzamidine Yield 84 %. Analytical data see table 1.

#### Synthesis method 9:

Aminobenzonitrile (1 eq.) and chlorosulfonylphenylisocyanate (1 eq) were dissolved in anhydrous dichloromethane under inert atmosphere and stirred at ambient temperature for 18 h. The precipitate was filtered off and dried in vacuo or else the reaction mixture was concentrated to dryness in vacuo. The dry substance (1 eq) was added to a solution of the benzylamine (1 - 2 eq.) and triethylamine (1 - 2 eq.) in anhydrous, acetonitrile at 0 °C under inert atmosphere. The reaction mixture was warmed to ambient temperature for 10 min and stirred for a further 18 h. It was then concentrated in vacuo, water was added and the resulting precipitate was filtered and

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dried in vacuo. Further reactions and purifications according to synthesis method 8.

**Synthesis of 3-{3-[4-(4-sulfamoyl-benzylsulfamoyl)-phenyl]-ureido}-benzamidine:**

A solution of 5.00 g (1 eq.) of 4-chlorosulfonylphenyl-isocyanate in anhydrous DCM (40 ml) was added to a solution of 3-aminobenzonitrile (2.71 g, 1 eq.) in anhydrous isocyanate (60 ml) at rt under inert atmosphere and the mixture was stirred overnight. The precipitate was filtered off to yield 7.3 g (95 %) of 4-[3-(3-cyanophenyl)-ureido]-benzenesulfonyl chloride.

4-[3-(3-Cyanophenyl)-ureido]-benzenesulfonylchloride (5.04 g, 1 eq.) was added in portions to a solution of 4-aminomethyl-benzenesulfonamide hydrochloride (6.68 g, 2 eq.) and triethylamine (8.32 ml, 2 eq.) in acetonitrile (100 ml) at 0 °C under inert atmosphere. The mixture was warmed to rt, stirred for 3 d and then concentrated in vacuo. Water was added and the resulting precipitate filtered off and dried in vacuo. Yield: 7.27 g (99.7 %) of [3-(3-cyanophenyl)-ureido]-N-(4-sulfonamidobenzyl)-4-benzenesulfonamide.

[3-(3-cyanophenyl)-ureido]-N-(4-sulfonamidobenzyl)-4-benzenesulfonamide (1 g) was suspended in methanolic hydrochloric acid (100 ml) at 0 °C under inert atmosphere and stirred for 20 h during which the mixture warmed to rt. The solution was concentrated under reduced pressure and diethylether was added. The resulting precipitate was filtered off, washed with diethylether and dried in vacuo. Yield: 849 mg (78 %) of 3-{3-[4-(4-sulfamoylbenzylsulfamoyl)-phenyl]-ureido}-benzimidic acid methyl ester.

3-{3-[4-(4-Sulfamoyl-benzylsulfamoyl)-phenyl]-ureido}-benzamidine (849 mg) were dissolved in methanolic ammonia solution (5 ml, 7 M) and refluxed for 2 h. The precipitate was filtered off and dried in vacuo to yield 719 mg (87 %) of 3-{3-[4-(4-sulfamoyl-benzylsulfamoyl)-phenyl]-ureido}-benzamidine.

Analytical data see table 1.

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**Synthesis of 3-{3-[4-(3-trifluoromethyl-benzylsulfamoyl)-phenyl]-ureido}-benzamidine:**

3-Trifluoromethylbenzylamine (0.52 g, 1 eq.) was added to a solution of 4-[3-(3-cyanophenyl)-ureido]-benzenesulfonyl chloride (1 g, 1 eq.) and triethylamine (1.05 ml, 1.6 eq.) in acetonitrile (10 ml) under inert atmosphere. The mixture was stirred for 3 d, concentrated in vacuo and water was added. The resulting precipitate was filtered off and dried in vacuo to yield 1.37 g (97 %) of 4-[3-(3-cyanophenyl)-ureido]-N-(3-trifluoromethylbenzyl)-benzenesulfonamide.

4-[3-(3-Cyanophenyl)-ureido]-N-(3-trifluoromethylbenzyl)-benzenesulfonamide (500 mg) were suspended in methanolic hydrochloridic acid (75 ml) at 0 °C under inert atmosphere and stirred for 2 d during which the mixture warmed to rt. The solution was concentrated to dryness in vacuo. The residue was dissolved in methanolic ammonia solution (6 ml, 7 M), the solution was refluxed for 2 h, concentrated in vacuo and purified by column chromatography (silica gel, ethyl acetate/methanol 7/1). Yield: 319 mg of 3-{3-[4-(3-trifluoromethylbenzylsulfamoyl)-phenyl]-ureido}-benzamidine. Analytical data see table 1.

**Synthesis of 4-{3-[4-(4-sulfamoylbenzylsulfamoyl)-phenyl]-ureido}-benzamidine:**

4-Cyanophenylisocyanate (190 mg, 1.5 eq.) was added in portions to a solution of 4-amino-N-(4-sulfamoylbenzyl)-benzamide (300 mg) in anhydrous THF (20 ml) under inert atmosphere and the mixture was refluxed for 7 h. The resulting precipitate was filtered off and dried in vacuo. The dry substance (200 mg) was suspended in methanolic hydrochloridic acid (75 ml) at 0 °C under inert atmosphere and stirred overnight during which the mixture was warmed to rt. The solution was concentrated in vacuo and the resulting precipitate filtered off after 5 h of storage at 4 °C. After drying in vacuo overnight, the precipitate was suspended in methanolic ammonia solution (5 ml, 7 M) and the mixture was refluxed for 4 h, cooled to rt and the resulting precipitate filtered off and dried in vacuo. Yield: 110 mg (53 % over 2

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steps) of 4-{3-[4-(4-sulfamoylbenzylsulfamoyl)-phenyl]-ureido}-benzamidine. Analytical data see table 1.

**Synthesis of 4-{3-[4-(4,5-dihydro-1H-imidazol-2-yl)-phenyl]-ureido}-N-(4-sulfamoylbenzyl)-benzenesulfonamide:**

3-{3-[4-(4-Sulfamoylbenzylsulfamoyl)-phenyl]-ureido}-benzimidic acid methyl ester (130 mg, 1 eq.) was suspended in anhydrous ethanol (10 ml), ethylenediamine (0.1 ml, 5.7 eq.) was added and the mixture was refluxed for 16 h. The precipitate was filtered off, washed with diethylether and dried in vacuo. Yield: 60 mg (45 %) of 4-{3-[4-(4,5-dihydro-1H-imidazol-2-yl)-phenyl]-ureido}-N-(4-sulfamoylbenzyl)-benzenesulfonamide. Analytical data see table 1.

**Synthesis of 3-{3-[4-(2,3,6-trifluorobenzylsulfamoyl)-phenyl]-ureido}-benzamidine:**

4-[3-(3-Cyanophenyl)-ureido]-benzenesulfonyl chloride (1.0 g, 2.98 mmol) was dissolved in 20 ml THF, 2,3,6-trifluorobenzylamine (0.48 g, 2.98 mmol) and DIEA (0.52 ml, 2.98 mmol) were added and the solution was refluxed for about 3 h. The solvent was removed in vacuo and the residue crystallized with ethanol / water. The solid was filtered and dried in vacuo. Yield 94 % of 4-[3-(3-cyano-phenyl)-ureido]-N-(2,3,6-trifluorobenzyl)-benzenesulfonamide.

4-[3-(3-Cyanophenyl)-ureido]-N-(2,3,6-trifluoro-benzyl)-benzenesulfonamide (230 mg, 0.5 mmol) was dissolved in HCl/MeOH (25 ml, 7 M) at 0 °C under inert atmosphere and stirred overnight at rt. The solution was concentrated and dried in vacuo to yield 99 % of 3-{3-[4-(2,3,6-trifluorobenzyl-sulfamoyl)-phenyl]-ureido}-benzimidic acid methyl ester

3-{3-[4-(2,3,6-Trifluorobenzylsulfamoyl)-phenyl]-ureido}-benzimidic acid methyl ester (250 mg, 0.5 mmol) was dissolved in NH<sub>3</sub>/MeOH (15 ml, 7 M). The solution was stirred overnight at rt. Further 10 ml of NH<sub>3</sub>/MeOH (7 M) were added and the mixture stirred for 3 h at 65 °C. The solvents were evaporated and the solid residue purified by flash chromatography on silica gel with a gradient of AcOEt and MeOH. The fractions with the

desired product were collected, evaporated and the product crystallized from MeOH/Et<sub>2</sub>O. Yield 50 %. Analytical data see table 1.

**Synthesis of 3-[3-[4-(benzhydrylsulfamoyl)-phenyl]-ureido]-benzamidine**

N-Benzhydryl-4-[3-(3-cyanophenyl)-ureido]-benzenesulfonamide (500 mg, 1.04 mmol, synthesized according to general method 8) was diluted in a mixture of MeOH (35 ml) and toluene (10 ml). NH<sub>2</sub>OH-HCl (220 mg, 3.11 mmol) and DIPEA (0.9 ml) were added and the reaction was stirred at 60 °C. After complete turnover of the nitrile to the amidoxime (e.g. 1-2 d) the solvent was removed in vacuo. Inorganic salts were separated by filtration over silica. Thus the amidoxime and as byproduct the amide were obtained.

To a solution of the amidoxime in acetic acid (40 ml) and MeOH (80 ml), Ac<sub>2</sub>O (263 µl, 2.5 mmol) was added at 0 °C. As soon as the turnover of the amidoxime to the acetate (e.g. 30 min) was complete, zinc powder (327 mg, 5 eq) was added. After reduction to the amidine the solvent was removed in vacuo, and the precipitate was portioned between water and ethylacetate. The product was extracted with ethylacetate, the solvent of the combined organic layers was removed in vacuo and the amidine purified by chromatography (AcOEt/MeOH-gradient) to yield the amidine (14 %). <sup>1</sup>H-NMR (d<sub>2</sub>-MeOH): 5.54 (s, 1 H, Ph<sub>2</sub>CH), 7.11-7.21 (m, 10 H, Ph), 7.42 (ddd, J = 7.8, 1.8 and 1.1 Hz, 1 H, 4-H) 7.45-7.58 (m, 5 H, Ph), 7.69-7.78 (ddd, J = 8.1, 1.8 and 1.1 Hz, 1 H, 6-H), 8.02 (t, J = 1.8 Hz, 1 H, 2-H).

**Biological activity**

For the determination of the antiplasmodial action of the compounds, the multiresistant Dd2 strain of *Plasmodium falciparum* was used. The incorporation of [8-<sup>3</sup>H]hypoxanthine into the parasitic nucleic acids was measured. The plasmodia

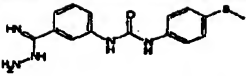
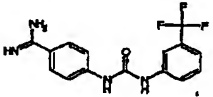
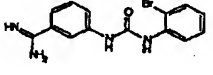
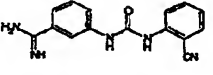
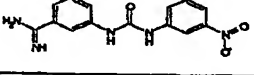
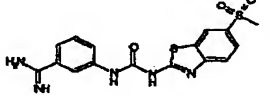
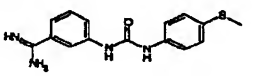
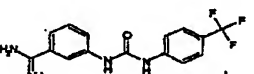
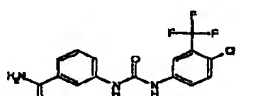
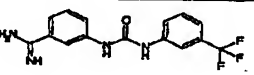
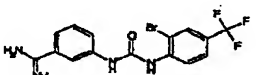
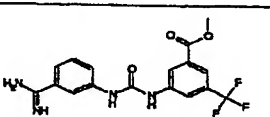
were incubated at 0.3% parasitaemia and an erythrocyte haematocrit of 2.5% in the presence of different concentrations of the compounds in a final volume of 200  $\mu$ l. The medium employed was RPMI 1640 which contained 10% of heat-treated human serum and 3 mg/l of gentamycin. In the incubations, the concentrations of the compounds varied from 0.3 to 100  $\mu$ M. After 48 h, each batch was treated with 50  $\mu$ l of [8-<sup>3</sup>H]hypoxanthine (1 mCi/ml) and incubated for a further 18 h. The cells were filtered off, washed and suspended in 20  $\mu$ l of scintillation fluid. The radioactive hypoxanthine absorbed by the parasites was then quantified using a scintillation counter.

The results were presented graphically and the  $IC_{50}$  value was determined using a fitting function. The value  $IC_{50}$ , the 'inhibition constant', indicates the value in  $\mu$ Mol/l at which 50% inhibition occurs.

Antiplasmodial activity against the 3D7 chloroquine sensitive strain of *Plasmodium falciparum* was determined as described elsewhere (J. Med. Chem. (2001) 44(19), 3187 - 3194).

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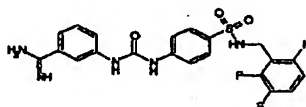
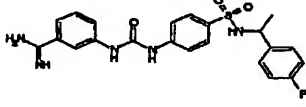
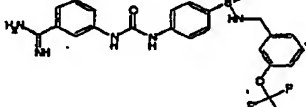
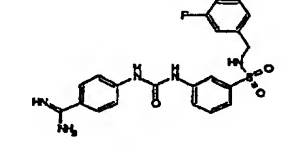
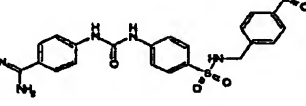
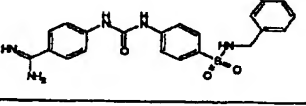
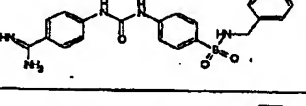
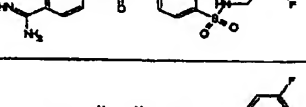
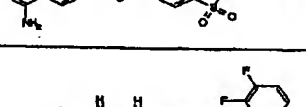

**Table 1:** Examples of the structures, analytical data and *in vitro* antiplasmodial activity of tested compounds (activity is defined A: IC50 value < 1  $\mu$ M; B: IC50 value 1 - 10  $\mu$ M; C: IC50 value 10 - 100  $\mu$ M). For abbreviations used see section "Examples".

|    |   |   |           |     |  |  |   |   |
|----|---|---|-----------|-----|--|--|---|---|
| 1  |    | 2 | 316 [M+H] | 316 |  |  | B |   |
| 2  |    | 2 | 323 [M+H] | 322 |  |  | B |   |
| 3  |    | 2 | 334 [M+H] | 333 |  |  | B |   |
| 4  |    | 4 | 290 [M+H] | 279 |  |  | B |   |
| 5  |    | 4 | 300 [M+H] | 299 |  |  | C | B |
| 6  |    | 4 | 390 [M+H] | 389 |  |  | C |   |
| 7  |   | 2 | 301 [M+H] | 300 |  |  | B |   |
| 8  |  | 4 | 323 [M+H] | 322 |  |  | B |   |
| 9  |  | 4 | 358 [M+H] | 357 |  |  | A |   |
| 10 |  | 4 | 323 [M+H] | 322 |  |  | B | B |
| 11 |  | 4 | 402 [M+H] | 401 |  |  | B |   |
| 12 |  | 4 | 391 [M+H] | 380 |  |  | B |   |

|    |  |   |                        |       |   |  |   |   |
|----|--|---|------------------------|-------|---|--|---|---|
| 13 |  | 4 | 391 [M+H]<br>389 [M-H] | 390   |   |  | B | B |
| 14 |  | 4 | 413 [M+H]              | 412   |   |  | B |   |
| 15 |  | 4 | 391 [M+H]<br>389 [M-H] | 390   |   |  | B | B |
| 16 |  | 4 | 381 [M+H]<br>379 [M-H] | 380   |   |  | B |   |
| 17 |  | 4 | 335 [M+H]              | 337   |   |  | C |   |
| 18 |  | 4 | 343 [M+H]              | 342   |   |  | A | A |
| 19 |  | 4 | 370 [M+H]              | 368   |   |  | B |   |
| 20 |  | 3 | 460 [M+H]              | 460,6 |   |  | B |   |
| 21 |  | 3 | 390 [M+H]              | 389   |   |  | B |   |
| 22 |  | 3 | 468 [M+H]              | 467,6 |   |  | C |   |
| 23 |  | 3 | 500 [M+H]              | 499,6 | 5.54 (s, 1 H, PhCH), 7.11-7.21 (m, 10 H, Ar-H), 7.42 (dd, J = 7.2, 1.6 and 1.1 Hz, 1 H, 4-H), 7.45-7.58 (m, 8 H, Ar-H), 7.60-7.78 (dd, J = 8.1, 1.6 and 1.1 Hz, 1 H, 6-H), 8.02 (t, J = 1.6 Hz, 1 H, 2-H) |  | A |   |
| 24 |  | 4 | 334 [M+H]              | 333   |   |  | C | C |
| 25 |  | 4 | 378 [M+H]              | 377   |   |  | A | B |

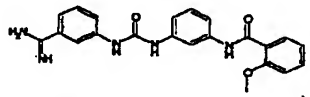
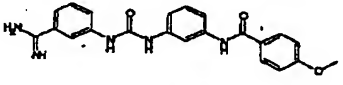
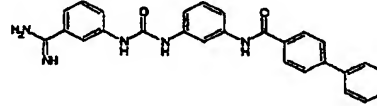
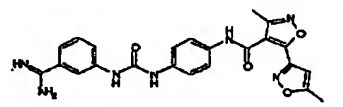
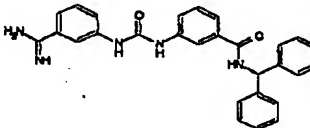
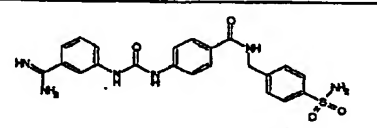
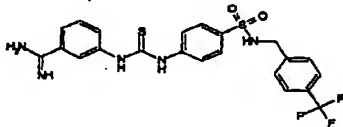
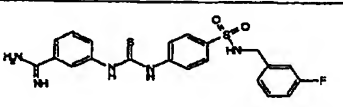
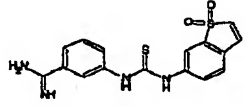
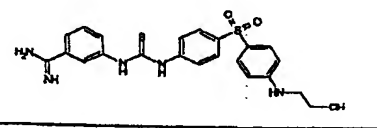
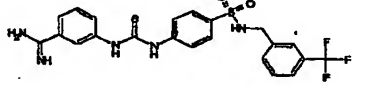
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|----|--|----|--|-------|---|--|---|---|
| 26 |  | 3  | 410 [M+H] <sup>+</sup>   | 409   |   |  | B |   |
| 27 |  | 3  | 546 [M+H] <sup>+</sup>   | 545.6 |   |  | B |   |
| 28 |  | 4  | 376 [M+H] <sup>+</sup>   | 376   |   |  | B |   |
| 29 |  | 3  | 461 [M+H] <sup>+</sup>   | 460.5 |   |  | B |   |
| 30 |  | 4  | 334 [M+H] <sup>+</sup>   | 333   |   |  | B |   |
| 31 |  | 4  | 424 [M+H] <sup>+</sup>   | 426   |   |  | B |   |
| 32 |  | 2a | 424 [M+H] <sup>+</sup>   | 423   |   |  | C |   |
| 33 |  | 6  | 424 [M+H] <sup>+</sup> , 1H NMR, 100-NMR, CHN Analyse              | 423   | 3.96 (d, J = 8.3, 2H, CH <sub>2</sub> ), 7.21-7.30 (m, 5H, Ar-H), 7.37 (d, J = 8.1, 1H, Ar-H), 7.52 (t, J = 7.6, 1H, Ar-H), 7.54 (d, J = 8.0, 2H, Ar-H), 7.71-7.78 (m, 3H, Ar-H), 7.95 (d, J = 2.1, 1H, Ar-H), 7.99 (t, J = 6.3, 1H, N-H), 9.13 (s, 2H, N-H), 9.38 (s, 2H, N-H), 10.08 (s, 1H, N-H), 10.23 (s, 1H, N-H) | 46.6 (CH <sub>2</sub> ), 117.4, 117.6, 121.3, 123.2, 127.4, 127.9, 128.2, 128.5, 129.5, 130.0, 133.5, 136.2, 140.5, 143.6 (C-Ar), 162.9 (C=O), 166.6 (C=N) | A |   |
| 34 |  | 9  | 508 [M+H] <sup>+</sup><br>506 [M+H] <sub>2</sub>                   | 507   |   |  | A | B |
| 35 |  | 9  | 503 [M+H] <sup>+</sup><br>501 [M+H] <sub>2</sub> , 1H NMR, 100-NMR | 503   | 3.96 (s, 2H, CH <sub>2</sub> ), 7.29-7.39 (m, 3H, Ar-H), 7.45-7.50 (m, 1H, Ar-H), 7.59-7.69 (m, 7H, Ar-H), 7.89 (s, 1H, Ar-H), 9.78 (s, 1H, N-H), 9.99 (s, 1H, N-H)   | 45.9 (CH <sub>2</sub> ), 117.4, 118.0, 121.2, 121.5, 125.9, 128.2, 129.3, 132.9, 133.2, 134.3, 139.9, 142.4, 143.9 (C-Ar), 162.7 (C=O), 164.6 (C=N)        | A |   |
| 36 |  | 6  | 442 [M+H] <sup>+</sup><br>440 [M+H] <sub>2</sub> , 1H NMR          | 441   | 4.00 (s, 2H, CH <sub>2</sub> ), 7.02-7.11 (m, 3H, Ar-H), 7.29-7.34 (m, 1H, Ar-H), 7.37 (d, J = 8.1, 1H, Ar-H), 7.54 (t, J = 8.1, 1H, Ar-H), 7.66 (s, J = 8.0, 2H, Ar-H), 7.75-7.78 (m, 3H, Ar-H), 7.96 (s, 1H, Ar-H), 9.20 (s, broad, 3H, N-H), 10.13 (s, 1H, N-H), 10.28 (s, 1H, N-H)                                  |  | A |   |

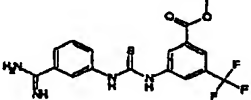
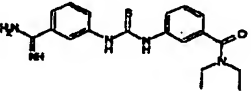
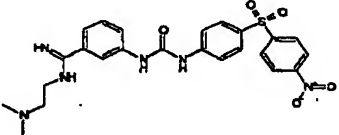
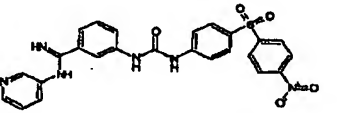
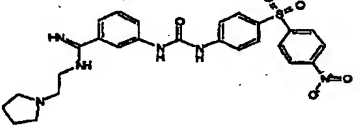
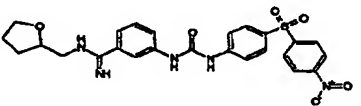
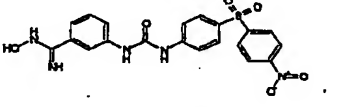
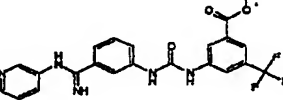
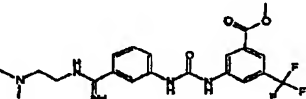
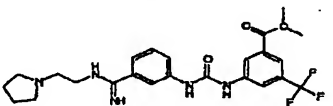
|    |  |   |   |     |   |   |  |
|----|--|---|---|-----|---|---|--|
| 37 |  | 9 | 482[M+H]<br>480[M+H], 1H-NMR              | 491 | 4.10 (s, 2 H, CH <sub>2</sub> ), 7.58 (d, J = 8.4, 1 H, Ar-H), 7.51 - 7.58 (m, 5 H, Ar-H), 7.53 (d, J = 8.1, 2 H, Ar-H), 7.70 - 7.78 (m, 3 H, Ar-H), 7.96 (s, 1 H, Ar-H), 9.24 (s, broad, 3 H, N-H), 10.03 (s, 1 H, N-H), 10.18 (s, 1 H, N-H)   | A |  |
| 38 |  | 9 | 482[M+H]<br>480[M+H], 1H-NMR              | 491 | 4.07 (s, 2 H, CH <sub>2</sub> ), 7.58 (d, J = 8.2, 1 H, Ar-H), 7.48 - 7.57 (m, 3 H, Ar-H), 7.64 - 7.67 (m, 4 H, Ar-H), 7.72 - 7.77 (m, 3 H, Ar-H), 7.96 (s, 1 H, Ar-H), 9.18 (s, broad, 3 H, N-H), 10.03 (s, 1 H, N-H), 10.19 (s, 1 H, N-H)   | A |  |
| 39 |  | 9 | 442[M+H]<br>440[M+H], 1H-NMR              | 441 | 3.96 (s, 2 H, CH <sub>2</sub> ), 7.10 (t, J = 9.0, 2 H, Ar-H), 7.28 (dd, J = 8.5, J = 5.5, 2 H, Ar-H), 7.37 (d, J = 8.3, 1 H, Ar-H), 7.54 (t, J = 8.0, 1 H, Ar-H), 7.65 (d, J = 8.1, 2 H, Ar-H), 7.70 - 7.76 (m, 3 H, Ar-H), 7.96 (s, 1 H, Ar-H), 9.26 (s, broad, 3 H, N-H), 10.03 (s, 1 H, N-H), 10.23 (s, 1 H, N-H)                 | A |  |
| 40 |  | 9 | 442[M+H]<br>440[M+H], 1H-NMR              | 441 | 4.00 (s, 2 H, CH <sub>2</sub> ), 7.06 - 7.16 (m, 2 H, Ar-H), 7.29 - 7.39 (m, 3 H, Ar-H), 7.54 (t, J = 8.0, 1 H, Ar-H), 7.65 (d, J = 8.0, 2 H, Ar-H), 7.71 - 7.78 (m, 3 H, Ar-H), 7.96 (s, 1 H, Ar-H), 9.26 (s, broad, 3 H, N-H), 9.52 (s, 1 H, N-H), 9.95 (s, 1 H, N-H)   | A |  |
| 41 |  | 9 | 478 [M+H]                                 | 477 | 3.99 (s, 2 H, CH <sub>2</sub> ), 7.29 - 7.73 (m, 10H, Ar and SO <sub>2</sub> -NH), 7.95 (s, 1H, Ar), 9.18 (m broad, 3H, CO-NH-NH-2), 9.59 (s, 1H, Urea NH), 9.62 (s, 1H, Urea NH)   | B |  |
| 42 |  | 9 | 480[M+H]<br>468[M+H], 1H-NMR              | 469 | 4.02 (s, 2 H, CH <sub>2</sub> ), 7.11 - 7.18 (m, 3 H, Ar-H), 7.37 (d, J = 8.3, 1 H, Ar-H), 7.54 (t, J = 8.0, 1 H, Ar-H), 7.63 (d, J = 8.1, 2 H, Ar-H), 7.69 - 7.78 (m, 3 H, Ar-H), 7.96 (s, 1 H, Ar-H), 9.05 (s, broad, 3 H, N-H), 9.83 (s, 1 H, N-H), 9.97 (s, 1 H, N-H)   | A |  |
| 43 |  | 9 | 480[M+H]<br>468[M+H]<br>1H-NMR            | 469 | 3.98 (d, J = 8.3, 2 H, CH <sub>2</sub> ), 7.58 (m, 3 H, Ar-H), 7.22 - 7.38 (m, 3 H, Ar-H), 7.54 (t, J = 8.0, 1 H, Ar-H), 7.63 (d, J = 8.1, 2 H, Ar-H), 7.69 - 7.78 (m, 3 H, Ar-H), 7.96 (s, 1 H, Ar-H), 9.05 (s, broad, 3 H, N-H), 9.81 (s, 1 H, N-H), 9.95 (s, 1 H, N-H)   | B |  |
| 44 |  | 9 | 480[M+H]<br>468[M+H]<br>1H-NMR            | 469 | 3.99 (s, 2 H, CH <sub>2</sub> ), 7.09 - 7.12 (m, 1 H, Ar-H), 7.22 - 7.38 (m, 3 H, Ar-H), 7.54 (t, J = 8.0, 1 H, Ar-H), 7.63 (d, J = 8.1, 2 H, Ar-H), 7.69 - 7.78 (m, 3 H, Ar-H), 7.96 (s, 1 H, Ar-H), 9.10 (s, broad, 3 H, N-H), 9.81 (s, 1 H, N-H), 9.95 (s, 1 H, N-H)   | B |  |
| 45 |  | 9 | 480[M+H]<br>468[M+H]<br>1H-NMR<br>180-NMR | 469 | 3.94 (d, J = 8.7, 2 H, CH <sub>2</sub> ), 6.97 (t, J = 8.0, 2 H, Ar-H), 7.25 - 7.38 (m, 2 H, Ar-H), 7.49 (t, J = 8.0, 1 H, Ar-H), 7.58 (d, J = 8.0, 2 H, Ar-H), 7.65 (d, J = 8.0, 2 H, Ar-H), 7.68 - 7.71 (m, 1 H, Ar-H), 7.81 - 7.84 (m, 2 H, Ar-H), 7.96 (s, 2 H, N-H), 9.22 (s, 2 H, N-H), 9.91 (s, 1 H, N-H), 10.05 (s, 1 H, N-H) | A |  |
| 46 |  | 9 | 510 [M+H]                                 | 509 |   | B |  |

|    |   |   |                                  |     |   |  |   |  |
|----|---|---|----------------------------------|-----|---|--|---|--|
| 47 |    | 9 | 478 [M+H]<br>1H-NMR              | 477 | 4.03 (s, 2H, CH <sub>2</sub> ); 7.02-7.10 (m, 1H, Ar); 7.35-7.70 (m, 5H, Ar); 7.96 (s, 1H, Ar); 8.10 (s, broad, 1H, SO <sub>2</sub> NH); 9.01-9.23 (m, broad, 3H, C(=O)NH <sub>2</sub> ); 9.88 (s, broad, 1H, Urea NH); 9.99 (s, broad, 1H, Urea NH)  | A  |   |  |
| 48 |    | 9 | 456 [M+H]<br>454 [M+H]           | 456 |   | B  |   |  |
| 49 |    | 9 | 508 [M+H]                        | 507 |   | B  |   |  |
| 50 |    | 9 | 442 [M+H]<br>440 [M+H]<br>1H-NMR | 441 | 4.03 (d, J = 8.0, 1H, CH <sub>2</sub> ), 7.02-7.12 (m, 5H, Ar+H), 7.29-7.33 (m, 1H, Ar+H), 7.39-7.43 (m, 1H, Ar+H), 7.49 (t, J = 7.5, 1H, Ar+H), 7.57-7.69 (m, 1H, Ar+H), 7.70 (d, J = 8.5, 2H, Ar+H), 7.81 (d, J = 9.0, 2H, Ar+H), 8.10 (s, 1H, Ar+H), 8.29 (s, broad, 1H, N+H), 8.84 (s, broad, 2H, N+H), 9.18 (s, broad, 2H, N+H), 9.67 (s, 1H, N+H), 10.04 (s, 1H, N+H) | A  |   |  |
| 51 |    | 9 | 503 [M+H]<br>501 [M+H]<br>1H-NMR | 503 | 4.02 (s, 2H, CH <sub>2</sub> ), 7.41-7.78 (m, 16H, Ar+H, N+H)   | 46.6 (CH <sub>2</sub> ), 117.4, 117.7, 125.6, 127.3, 127.59, 127.72, 129.3, 133.1, 140.9, 142.0, 149.0, 149.3 (C-Ar), 152.1 (C=O), 162.1 (C-N) | A |  |
| 52 |   | 9 | 442 [M+H]<br>440 [M+H]<br>1H-NMR | 441 | 4.00 (s, 2H, CH <sub>2</sub> ), 7.01-7.11 (m, 3H, Ar+H), 7.29-7.36 (m, 1H, Ar+H), 7.62-7.74 (m, 5H, Ar+H), 7.82 (d, J = 8.5, 2H, Ar+H), 8.09 (s, 1H, N+H), 10.02 (s, 1H, N+H), 10.10 (s, 1H, N+H)   | A  |   |  |
| 53 |  | 9 | 442 [M+H]<br>440 [M+H]<br>1H-NMR | 441 | 3.95 (d, J = 5.5, 2H, CH <sub>2</sub> ), 7.11 (t, J = 8.5, 2H, Ar+H), 7.29 (dd, J = 8.7, J = 5.5, 2H, Ar+H), 7.83-7.84 (m, 6H, Ar+H), 7.89 (d, J = 8.5, 2H, Ar+H), 8.02 (t, J = 8.1, 1H, N+H), 8.85 (s, 2H, N+H), 9.21 (s, 2H, N+H), 10.21 (s, 1H, N+H), 10.30 (s, 1H, N+H)   | A  |   |  |
| 54 |  | 9 | 460 [M+H]<br>458 [M+H]<br>1H-NMR | 459 | 3.99 (s, 2H, CH <sub>2</sub> ), 7.01 (t, J = 8.0, 2H, Ar+H), 7.31-7.41 (m, 1H, Ar+H), 7.49 (d, J = 8.7, 2H, Ar+H), 7.61 (d, J = 8.5, 2H, Ar+H), 7.67-7.74 (m, 4H, Ar+H)   | A  |   |  |
| 55 |  | 9 | 460 [M+H]<br>458 [M+H]<br>1H-NMR | 459 | 3.98 (s, 1H, CH <sub>2</sub> ), 7.02 (ddd, J = 8.5, J = 8.5, J = 2.5, 1H, Ar+H), 7.11-7.16 (ddd, J = 8.5, J = 8.5, J = 2.5, 1H, Ar+H), 7.69 (ddd, J = 8.5, J = 8.5, J = 8.5, 1H, Ar+H), 7.62-7.70 (m, 6H, Ar+H), 7.82 (d, J = 8.5, 2H, Ar+H), 8.02 (s, broad, 1H, N+H), 8.95 (s, 1H, N+H), 10.02 (s, 1H, N+H)   | A  |   |  |
| 56 |  | 9 | 478 [M+H]<br>476 [M+H]<br>1H-NMR | 477 | 4.01 (d, J = 5.5, 2H, CH <sub>2</sub> ), 7.01-7.07 (m, 1H, Ar+H), 7.34-7.46 (m, 1H, Ar+H), 7.61 (d, J = 8.5, 2H, Ar+H), 7.68 (d, J = 7.5, 4H, Ar+H), 7.81 (d, J = 8.0, 2H, Ar+H), 8.10 (t, J = 8.5, 1H, N+H), 8.92 (s, 2H, N+H), 9.20 (s, 2H, N+H), 10.13 (s, 1H, N+H), 10.23 (s, 1H, N+H)  | A  |   |  |

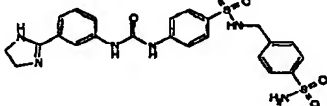
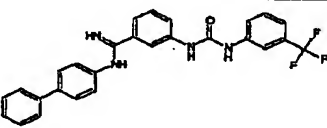
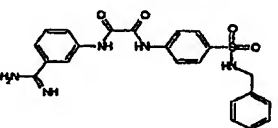
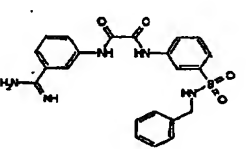


|    |  |   |  |       |   |   |   |
|----|--|---|--|-------|---|---|---|
| 57 |  | 8 | 442 [M+H] <sup>+</sup><br>440 [M+H] <sup>+</sup><br>1H-NMR | 441   | 4.09 (d, J = 6.2, 2 H, CH <sub>2</sub> ), 7.02-7.12 (m, 8 H, Ar-H), 7.29-7.41 (m, 3 H, Ar-H), 7.46-7.59 (m, 3 H, Ar-H), 7.73 (d, J = 8.3, 1 H, Ar-H), 7.98 (s, 1 H, Ar-H), 8.12 (t, J = 1.9, 1 H, Ar-H), 8.27 (m, broad, 1 H, N-H), 9.00 (s, broad, 2 H, N-H), 9.85 (s, broad, 2 H, N-H), 9.79 (s, broad, 2 H, N-H) | B |   |
| 58 |  | 8 | 503 [M+H] <sup>+</sup><br>501 [M+H] <sup>+</sup><br>1H-NMR | 503   | 4.06 (d, J = 6.1, 2 H, CH <sub>2</sub> ), 7.23-7.51 (m, 8 H, Ar-H), 7.62 (d, J = 8.5, 1 H, Ar-H), 7.73-7.78 (m, 3 H, Ar-H), 7.99 (t, J = 1.7, 1 H, Ar-H), 8.17 (t, J = 1.9, 1 H, Ar-H), 8.56 (s, broad, 4 H, N-H), 10.4 (s, broad, 2 H, N-H)  | B |   |
| 59 |  | 9 | 469 [M+H] <sup>+</sup><br>467 [M+H] <sup>+</sup>           | 469   |   | A |   |
| 60 |  | 3 | 529 [M+H] <sup>+</sup>                                     | 529.0 |   | B |   |
| 61 |  | 4 | 393 [M+H] <sup>+</sup>                                     | 394   |   | B | B |
| 62 |  | 4 | 395 [M+H] <sup>+</sup>                                     | 394   |   | B | B |
| 63 |  | 8 | 440 [M+H] <sup>+</sup>                                     | 439   | 7.36 (d, J = 6.2, 1 H, Ar-H), 7.51 (t, J = 6.0, 1 H, Ar-H), 7.66-7.73 (m, 3 H, Ar-H), 7.82-7.96 (m, 3 H, Ar-H), 8.17 (d, J = 9.1, 2 H, Ar-H), 8.38 (d, J = 9.1, 2 H, Ar-H), 9.07 (s, broad, 3 H, N-H), 9.72 (s, broad, 1 H, N-H)  | A |   |
| 64 |  | 4 | 396 [M+H] <sup>+</sup><br>393 [M+H] <sup>+</sup>           | 394   |   | A | B |
| 65 |  | 4 | 464 [M+H] <sup>+</sup>                                     | 463.5 |   | B |   |
| 66 |  | 4 | 312 [M+H] <sup>+</sup>                                     | 311   |   | B |   |
| 67 |  | 4 | 404 [M+H] <sup>+</sup>                                     | 403.4 |   | B | B |

|    |   |    |  |       |  |  |   |  |
|----|---|----|--|-------|--|--|---|--|
| 68 |    | 2  | 404 [M+H] <sup>+</sup>                           | 403   |  |  | B |  |
| 69 |    | 2  | 404 [M+H] <sup>+</sup>                           | 403   |  |  | A |  |
| 70 |    | 2a | 450 [M+H] <sup>+</sup>                           | 449,5 |  |  | B |  |
| 71 |    | 2a | 480 [M+H] <sup>+</sup>                           | 459   |  |  | B |  |
| 72 |    | 2  | 464 [M+H] <sup>+</sup>                           | 463,5 |  |  | B |  |
| 73 |    | 8  | 468 [M+H] <sup>+</sup>                           | 467   |  |  | B |  |
| 74 |   | 4a | 508 [M+H] <sup>+</sup>                           | 507,6 |  |  | A |  |
| 75 |  | 4a | 457 [M+H] <sup>+</sup>                           | 458   |  |  | A |  |
| 76 |  | 4a | 359 [M+H] <sup>+</sup>                           | 358   |  |  | A |  |
| 77 |  | 4a | 469 [M+H] <sup>+</sup>                           | 470   |  |  | B |  |
| 78 |  | 4a | 508 [M+H] <sup>+</sup><br>509 [M+H] <sup>+</sup> | 507,8 |  |  | A |  |

|    |   |    |                         |       |  |  |   |  |
|----|---|----|-------------------------|-------|--|--|---|--|
| 79 |    | 4a | 397 [M+H]               | 396   |  |  | A |  |
| 80 |    | 4a | 370 [M+H]               | 369   |  |  | A |  |
| 81 |    | 7  | 611 [M+H],<br>609 [M+H] | 610,6 |  |  | B |  |
| 82 |    | 7  | 617 [M+H]               | 616,6 |  |  | A |  |
| 83 |    | 7  | 637 [M+H],<br>636 [M+H] | 636,6 |  |  | B |  |
| 84 |    | 7  | 624 [M+H],<br>622 [M+H] | 623,6 |  |  | B |  |
| 85 |  | 7  | 466 [M+H],<br>464 [M+H] | 466   |  |  | A |  |
| 86 |  | 7  | 466 [M+H]               | 467   |  |  | B |  |
| 87 |  | 7  | 462 [M+H]               | 461   |  |  | B |  |
| 88 |  | 7  | 478 [M+H]               | 480   |  |  | B |  |

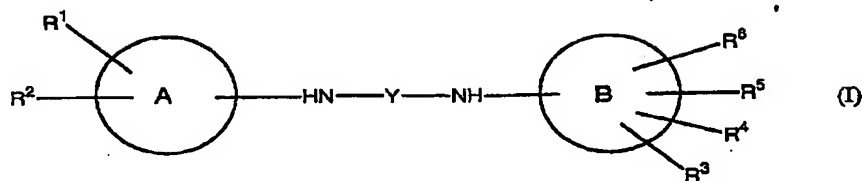
|    |  |   |   |     |  |  |   |  |
|----|--|---|---|-----|--|--|---|--|
| 89 |  | 8 | 680 [M+H]<br>676 [M+H]                      | 680 |  |  | B |  |
| 90 |  | 8 | 616 [M+H]<br>614 [M+H]<br>1H-NMR            | 616 | 2.66 (t, J = 6.2, 2 H, NCH <sub>2</sub> ), 3.25 (s, 4H, NCH <sub>2</sub> ), 3.47 (t, J = 6.2, 2 H, NCH <sub>2</sub> ), 3.54 (t, J = 4.5, 4 H, OCH <sub>2</sub> ), 3.90 (s, 2 H, BrCH <sub>2</sub> ), 7.22 - 7.39 (m, 3 H, Ar-H), 7.47 (t, J = 7.9, 1 H, Ar-H), 7.69 - 7.89 (m, 7 H, Ar-H), 7.97 (s, 1 H, Ar-H), 9.07 (s, broad, 1 H, N-H), 9.87 (s, 1 H, N-H), 10.00 (s, 1 H, N-H) |  | A |  |
| 91 |  | 7 | 349 [M+H]<br>347 [M+H]<br>1H-NMR<br>13C-NMR | 348 | 3.61 (s, 4 H, NCH <sub>2</sub> CH <sub>2</sub> N), 7.29 - 7.41 (m, 3 H, Ar-H), 7.47 - 7.63 (m, 3 H, Ar-H), 7.89 (s, 1 H, Ar-H), 8.05 (s, 1 H, Ar-H), 9.61 (s, 1 H, N-H), 9.69 (s, 1 H, N-H)  |  | A |  |
| 92 |  | 7 | 339 [M+H]<br>337 [M+H]                      | 338 |  |  |   |  |
| 93 |  | 7 | 430 [M+H]<br>434 [M+H]                      | 435 |  |  | B |  |
| 94 |  | 8 | 608 [M+H]<br>606 [M+H]                      | 607 | 4.09 (d, J = 6.8, 2 H, CH <sub>2</sub> ), 5.79 (s, 2 H, N-H), 7.27-7.29 (m, 2 H, Ar-H), 7.46 - 7.61 (m, 2 H, Ar-H), 7.63 - 7.69 (m, 3 H, Ar-H), 7.89 (s, J = 9.0, 2 H, Ar-H), 7.99 (d, J = 9.0, 2 H, Ar-H), 7.77 (s, 1 H, Ar-H), 8.11, (t, J = 6.1, 1 H, N-H), 8.93 (s, 1 H, N-H), 9.08 (s, 1 H, N-H), 9.80 (s, 1 H, O-H)  |  |   |  |
| 95 |  | 8 | 440 [M+H]                                   | 439 |  |  |   |  |
| 96 |  | 8 | 619 [M+H]<br>617 [M+H]                      | 618 | 4.03 (d, J = 6.5, 2 H, CH <sub>2</sub> ), 5.76 (s, 2 H, N-H), 7.29 - 7.31 (m, 4 H, Ar-H, N-H), 7.43 - 7.62 (m, 3 H, Ar-H), 7.85 (d, J = 9.0, 2 H, Ar-H), 7.73 - 7.78 (m, 3 H, Ar-H), 8.08 (t, J = 6.2, 1 H, N-H), 8.87 (s, 1 H, N-H), 9.13 (s, 1 H, N-H), 9.62 (s, 1 H, O-H)   | 45.7 (C-F), 115.9, 117.9, 119.3, 119.8, 125.8, 128.0, 128.7, 132.8, 134.3, 138.2, 142.8, 143.1, 143.7 (C-Ar), 151.1 (C=O), 152.4 (C-N) | B |  |
| 97 |  | 8 | 607 [M+H]<br>605 [M+H]                      | 606 |  |  |   |  |
| 98 |  | 8 | 661 [M+H]                                   | 660 |  |  |   |  |

|     |   |   |  |       |   |  |   |  |
|-----|---|---|--|-------|---|--|---|--|
| 99  |  | 6 | 529 [M+H] <sup>+</sup><br>527 [M+H] <sup>+</sup> | 529   | 3.80 (s, 4 H, NCH <sub>2</sub> CH <sub>2</sub> N), 4.02 (s, 2 H, BrCH <sub>2</sub> ), 7.31 - 7.46 (m, 8 H, Ar-H), 7.58 (m, 1 H, Ar-H), 7.64 - 7.78 (m, 6 H, Ar-H), 7.88 (s, 1 H, Ar-H), 8.00 (s, 1 H, N-H), 8.23 (s, 1 H, N-H)  |  | A |  |
| 100 |  | 7 | 473 [M+H] <sup>+</sup><br>475 [M+H] <sup>+</sup> | 474   |   |  | B |  |
| 101 |  | 7 | 452 [M+H] <sup>+</sup>                           | 451.8 | 4.07 (s, 2 H, BrCH <sub>2</sub> ), 7.18-7.26 (m, 6 H, Ph), 7.59 (dt, J = 7.8 and 1.7 Hz, 1 H, 4-H), 7.84 (t, J = 7.8 Hz, 1 H, 5-H), 7.83 (dt, J = 9.0 and 2.1 Hz, 2 H, 3',5'-H), 7.96 (dt, J = 8.0 and 2.1 Hz, 2 H, 2',6'-H), 7.69 (dt, J = 7.8 and 1.7 Hz, 1 H, 6-H), 8.13 (t, J = 1.7 Hz, 1 H, 2-H) | 47.9 (CH <sub>2</sub> -Br), 120.7 (C-2), 121.5 (C-2'), 125.3 (C-4), 126.9 (C-6), 128.5 (C-4'), 128.9, 129.1 and 129.4 (C-3',5',2',6'), 131.2 (C-5), 130.5, 138.2, 138.5, 139.7 and 142.3 (C-1,3,1',2',7), 159.7 and 159.9 (C=O), 168.6 (C=N) | B |  |
| 102 |  | 7 | 452 [M+H] <sup>+</sup>                           | 451.6 | 4.02 (s, 2 H, PhCH <sub>2</sub> ), 7.16-7.30 (m, 6 H, Ph), 7.54-7.68 (m, 4 H), 8.07-8.08 (m, 1 H), 8.17 (dt, J = 7.1 and 2.0 Hz, 1 H), (aromatic), 8.29-8.31 (m, 1 H) and 8.44-8.46 (m, 1 H) (H-1 and H-1')   | 48.1 (CH <sub>2</sub> -Ph), 118.5 and 119.9 (C-1 and C-1'), 122.4, 124.0, 124.2, 125.2, 127.0, 127.5, 128.1, 128.0, 129.5, 129.6, 137.6, 138.0, 138.0 (C-aromatic), 156.0 and 158.6 (C=O-N), 166.1 (N=O-N)                                   | C |  |

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## Patent claims

## 1. Compounds of the formula (I)



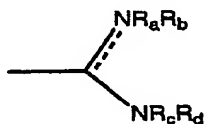
or a salt thereof, where

Y is C=O, C=S, C=NH, (C=O)<sub>2</sub> or SO<sub>2</sub>;

(A) and (B) are independently an aromatic hydrocarbon group which optionally contains one or more heteroatoms selected from the group consisting of S, O and N, wherein the heteroatom N is optionally substituted with R', the heteroatom S is optionally bond to =O or (=O)<sub>2</sub>;

R' is hydrogen, hydroxyalkyl, haloalkyl, aminoalkyl, alkoxy, cyanoalkyl, alkyl or an unsaturated or saturated carbocyclic group selected from the group consisting of cyclopentyl, cyclohexyl, aryl and heteroaryl;

R<sup>1</sup> is



where R<sub>a</sub> and R<sub>b</sub> are independently hydrogen, -O-(CO)-R' (where R' is as defined above), hydroxyl, hydroxyalkyl, haloalkyl, aminoalkyl, alkoxy, cyanoalkyl, alkyl or an unsaturated or saturated carbocyclic group selected from the group consisting of cyclopentyl, cyclohexyl, aryl, heteroaryl; R<sub>c</sub> is an optional substituent which may be independently of R<sub>a</sub> and R<sub>b</sub> and may be selected from the group as defined

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above for  $R_a$  and  $R_c$ ;  $R_a$  is hydrogen or one of the following groups:

$-(CO)-R_a$  where  $R_a$  is independently hydrogen, alkoxy, alkylthio, halogen, haloalkyl, haloalkyloxy, hydroxyalkyl, hydroxyalkylamino, alkyl, aryl, heteroaryl, amino, aminoalkyl or alkylamino group;

$-(CH_2)_n-R_a$  where  $R_a$  is independently hydrogen, a hydroxyalkyl, an alkyl, an allyl, an amino, an alkylamino, a morpholino, 2-tetrahydrofuran, N-pyrrolidino, a 3-pyridyl, a phenyl, a benzyl, a biphenyl or another heterocyclic group and  $n$  is 0, 1, 2 or 3;

$-NR_aR_c$  where  $R_a$  and  $R_c$  are defined above;

or  $R_a$  forms together with  $R_c$  a 5- or 6- membered unsaturated or saturated heterocyclic ring which optionally has 0 to 3 times substituents  $R''$ ;

the dotted line means a double bond unless there is a substituent  $R_a$  in the formula of  $R^1$  as defined above.

$R''$  is independently hydrogen, alkoxy, alkylthio, aminoalkyl halogen,  $-CO_2R'$ ,  $-CR'O$ , haloalkyl, haloalkyloxy,  $-NO_2$ ,  $-CN$ , hydroxyalkyl, alkyl, aryl, heteroaryl, amino, alkylamino or aminoalkyl group or a double bounded oxygen, wherein  $R'$  is as defined above;

$R^2$  is a hydrogen, a halogen, alkoxy, alkylthio,  $-CO_2R'$ ,  $-CR'O$ , haloalkyl, haloalkyloxy,  $-NO_2$ ,  $-CN$ , hydroxy, hydroxyalkyl, alkyl, aryl, amino, alkylamino or aminoalkyl group;

$R^3$  is a hydrogen, a halogen, haloalkyl,  $-NO_2$ ,  $-CN$ , alkyl or aryl group;

$R^4$  is a hydrogen or a group capable of hydrogen bond formation except for a group as defined for substituent  $R^1$ ;

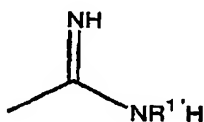
$R^5$  is hydrogen or, independently of  $R^4$ , a group selected from the groups as defined above for  $R^4$

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$R^6$  is hydrogen or, independently of  $R^3$ , a group selected from the groups as defined above for  $R^2$ ; and

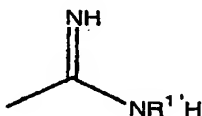
with the proviso that the compounds of the formula (I) are not compounds

in which Y is equal to C=O, both (A) and (B) are a phenyl group, R<sup>1</sup> is the group



where R<sup>1</sup> is hydrogen or phenyl, R<sup>2</sup>, R<sup>3</sup>, R<sup>5</sup> and R<sup>6</sup> are identical and are hydrogen, R<sup>4</sup> is phenyl, benzyl, phenoxy, chloro or dimethylamino group in the 3- or 4-position to the NH-Y-NH group of the compound of the formula(I);  
or compounds in which (A) and (B) are phenyl and R<sup>4</sup>, R<sup>5</sup> or R<sup>6</sup> are in the ortho-position to the NH-Y-NH group of the compound of the formula(I).

2. The compounds according to Claim 1 with the proviso that the compounds of the formula (I) are not compounds in which Y is equal to C=O, (B) is a benzofuranyl, dibenzofuranyl, 1-alkylindol or optionally by alkyl, halogen, trihaloalkoxy or N,N-dialkylamino substituted aryl, R<sup>1</sup> is the group

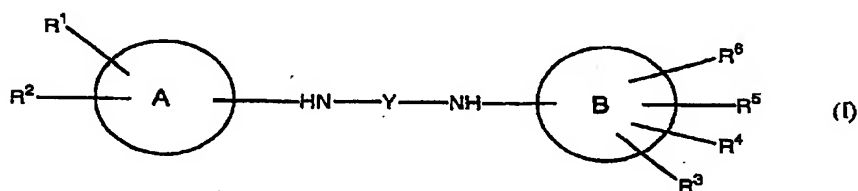


where R' is hydrogen, alkyl, acyl, aryl, 1-alkylindolyl or alkylthio.

3. The compounds according to Claim 1 or 2, characterized in that (A) and (B) are both a phenyl group.



4. The compounds according to one of the preceding claims, characterized in that  $R^2$ ,  $R^3$ ,  $R^5$  and /or  $R^6$  are hydrogen.
5. The compounds according to one of the preceding claims, characterized in that  $R^1$  is an optionally substituted or cyclic amidine.
6. The compounds according to one of the preceding claims, characterized in that  $R_a$  and/or  $R_b$  are hydrogen and/or  $R_c$  is not present.
7. The compounds according to one of the preceding claims, characterized in that  $R^4$  is a arylsulphone, sulphonamide, alkylsulphonamide, arylsulphonamide, alkylsulphone or benzylsulfonamide where the substituents are independently one or more of the following groups: hydrogen, halogen, haloalkyl, haloalkoxy,  $\text{CONRR}'$ ,  $\text{SO}_2\text{NRR}'$ ,  $\text{CO}_2\text{R}$  and sulphonamide, where  $R$  and  $R'$  independently are as defined above.
8. The compounds according to one of Claims 1 to 7 or a salt thereof as a medicament.
9. Process for the preparation of a compound according to anyone of Claims 1 to 7.
10. The use of a compound according to formula (I)



or a salt thereof, where

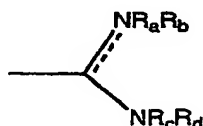
$Y$  is  $\text{C=O}$ ,  $\text{C=S}$ ,  $\text{C=NH}$ ,  $(\text{C=O})_2$  or  $\text{SO}_2$ ;

(A) and (B) are independently an aromatic hydrocarbon group

which optionally contains one or more heteroatoms selected from the group consisting of S, O and N, wherein the heteroatom N is optionally substituted with R', the heteroatom S is optionally bond to =O or (=O)<sub>2</sub>;

R' is hydrogen, hydroxyalkyl, haloalkyl, aminoalkyl, alkoxy, cyanoalkyl, alkyl or an unsaturated or saturated carbocyclic group selected from the group consisting of cyclopentyl, cyclohexyl, aryl and heteroaryl;

R<sup>i</sup> is



where R<sub>a</sub> and R<sub>b</sub> are independently hydrogen, -O-(CO)-R' (where R' is as defined above), hydroxyl, hydroxyalkyl, haloalkyl, aminoalkyl, alkoxy, cyanoalkyl, alkyl or an unsaturated or saturated carbocyclic group selected from the group consisting of cyclopentyl, cyclohexyl, aryl, heteroaryl; R<sub>c</sub> is an optional substituent which may be independently of R<sub>a</sub> and R<sub>b</sub> and may be selected from the group as defined above for R<sub>a</sub> and R<sub>b</sub>; R<sub>d</sub> is hydrogen or one of the following groups:

-(CO)-R<sub>e</sub> where R<sub>e</sub> is independently hydrogen, alkoxy, alkylthio, halogen, haloalkyl, haloalkyloxy, hydroxyalkyl, hydroxyalkylamino, alkyl, aryl, heteroaryl, amino, aminoalkyl or alkylamino group;

-(CH<sub>2</sub>)<sub>n</sub>-R<sub>f</sub> where R<sub>f</sub> is independently hydrogen, a hydroxyalkyl, an alkyl, an allyl, an amino, an alkylamino, a morpholino, 2-tetrahydrofuran, N-pyrrolidino, a 3-pyridyl, a phenyl, a benzyl, a biphenyl or another heterocyclic group and n is 0, 1, 2 or 3;

-NR<sub>g</sub>R<sub>h</sub> where R<sub>g</sub> and R<sub>h</sub> are defined above;

or R<sub>a</sub> forms together with R<sub>b</sub> a 5- or 6- membered unsaturated or saturated heterocyclic ring which optionally has 0 to 3 times substituents R'';

the dotted line means a double bond unless there is a substituent R<sub>g</sub> in the formula of R<sup>i</sup> as defined above.

- R'' is independently hydrogen, alkoxy, alkylthio, aminoalkyl halogen,  $-\text{CO}_2\text{R}'$ ,  $-\text{CR}'\text{O}$ , haloalkyl, haloalkyloxy,  $-\text{NO}_2$ ,  $-\text{CN}$ , hydroxyalkyl, alkyl, aryl, heteroaryl, amino, alkylamino or aminoalkyl group or a double bounded oxygen, wherein R' is as defined above;
- R<sup>2</sup> is a hydrogen, a halogen, alkoxy, alkylthio,  $-\text{CO}_2\text{R}'$ ,  $-\text{CR}'\text{O}$ , haloalkyl, haloalkyloxy,  $-\text{NO}_2$ ,  $-\text{CN}$ , hydroxy, hydroxyalkyl, alkyl, aryl, amino, alkylamino or aminoalkyl group;
- R<sup>3</sup> is a hydrogen, a halogen, haloalkyl,  $-\text{NO}_2$ ,  $-\text{CN}$ , alkyl or aryl group;
- R<sup>4</sup> is a hydrogen or a group capable of hydrogen bond formation except for a group as defined for substituent R<sup>1</sup>;
- R<sup>5</sup> is hydrogen or, independently of R<sup>4</sup>, a group selected from the groups as defined above for R<sup>4</sup>
- R<sup>6</sup> is hydrogen or, independently of R<sup>2</sup>, a group selected from the groups as defined above for R<sup>2</sup>;

with the proviso that the compounds of the formula (I) are not compounds in which (A) and (B) are phenyl and R<sup>4</sup>, R<sup>5</sup> or R<sup>6</sup> are in the ortho-position to the NH-Y-NH group of the compound of the formula(I);

for the preparation of a medicament for the treatment of diseases caused by protozoa.

11. The use according to Claim 10, wherein the compound are as defined in any one of the Claims 1-7.
12. The use according to Claim 10 or 11 for the treatment of malaria diseases.

13. A pharmaceutical composition comprising at least one compound according to one of Claims 1 to 7 or a salt thereof.

1002063-124201

ABSTRACT

Treatment of Protozoan Infections with new diphenylurea derivatives.

1002053-101204  
1002053-101204

PATENT  
ATTORNEY DOCKET NO: 50125/041001

**COMBINED DECLARATION AND POWER OF ATTORNEY**

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled **COMPOUNDS FOR THE TREATMENT OF PROTOZOAL DISEASE**, the specification of which

☒ is attached hereto.

☐ was filed on \_\_\_\_\_ as Application Serial No. \_\_\_\_\_  
and was amended on \_\_\_\_\_

☐ was described and claimed in PCT International Application No. \_\_\_\_\_  
filed on \_\_\_\_\_ and as amended under PCT Article 19 on \_\_\_\_\_

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose all information I know to be material to patentability in accordance with Title 37, Code of Federal Regulations, § 1.56.

**FOREIGN PRIORITY RIGHTS:** I hereby claim foreign priority benefits under Title 35, United States Code, § 119 of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

| Country | Serial Number   | Filing Date       | Priority Claimed? |
|---------|-----------------|-------------------|-------------------|
| Germany | DE 101 09 204.0 | February 26, 2001 | Yes               |

**PROVISIONAL PRIORITY RIGHTS:** I hereby claim priority benefits under Title 35, United States Code, § 119(e) and § 120 of any United States provisional patent application(s) listed below filed by an inventor or inventors on the same subject matter as the present application and having a filing date before that of the application(s) of which priority is claimed:

| Serial Number | Filing Date | Status |
|---------------|-------------|--------|
|               |             |        |

**NON-PROVISIONAL PRIORITY RIGHTS:** I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose all

### COMBINED DECLARATION AND POWER OF ATTORNEY

information I know to be material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application:

| Serial Number | Filing Date | Status |
|---------------|-------------|--------|
|               |             |        |
|               |             |        |

I hereby appoint the following attorneys and/or agents to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: Paul T. Clark, Reg. No. 30,162, Karen L. Elbing, Ph.D. Reg. No. 35,238, Kristina Bieker-Brady, Ph.D. Reg. No. 39,109, Susan M. Michaud, Ph.D. Reg. No. 42,885, James D. DeCamp, Ph.D., Reg. No. 43,580, Sean J. Edman, Reg. No. 42,506, Timothy J. Douros, Reg. No. 41,716.

Address all telephone calls to: Karen L. Elbing at 617/428-0200.

Address all correspondence to: Karen L. Elbing at Clark & Elbing LLP, 176 Federal Street, Boston, MA 02110. **Customer No: 21559**

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

| Full Name<br>(First, Middle, Last) | Residence Address<br>(City, State, Country) | Post Office Address<br>(Street, City, State, Country) | Citizenship |
|------------------------------------|---|---|-------------|
| Andrea Aschenbrenner               | Munchen, Germany                            | Steinerweg 1a, Munchen<br>GERMANY 81241               | German      |
| Signature:                         |   |   | Date:       |

| Full Name<br>(First, Middle, Last) | Residence Address<br>(City, State, Country) | Post Office Address<br>(Street, City, State, Country) | Citizenship |
|------------------------------------|---|---|-------------|
| Katharina Aulinger Fuchs           | Neuried, Germany                            | Hellerholz 3, Neuried<br>GERMANY 82061                | German      |
| Signature:                         |   |   | Date:       |

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| Full Name<br>(First, Middle, Last) | Residence Address<br>(City, State, Country) | Post Office Address<br>(Street, City, State, Country) | Citizenship |
|------------------------------------|---|---|-------------|
| Matthias Dormeyer                  | Munchen, Germany                            | Helene-Weber Allee 10<br>Munchen, GERMANY<br>80637    | German      |
| Signature:                         |   |   | Date:       |

| Full Name<br>(First, Middle, Last) | Residence Address<br>(City, State, Country) | Post Office Address<br>(Street, City, State, Country) | Citizenship |
|------------------------------------|---|---|-------------|
| Gabriel Garcia                     | Munchen, Germany                            | An der Rehwiese 15<br>Munchen, GERMANY<br>81375       | Mexican     |
| Signature:                         |   |   | Date:       |

| Full Name<br>(First, Middle, Last) | Residence Address<br>(City, State, Country) | Post Office Address<br>(Street, City, State, Country) | Citizenship |
|------------------------------------|---|---|-------------|
| Bernd Kramer                       | Aachen, Germany                             | Apploniastraße 56<br>Aachen, GERMANY 52080            | German      |
| Signature:                         |   |   | Date:       |

| Full Name<br>(First, Middle, Last) | Residence Address<br>(City, State, Country) | Post Office Address<br>(Street, City, State, Country)       | Citizenship |
|------------------------------------|---|---|-------------|
| Stefano Pegoraro                   | Planegg-Martinsried,<br>Germany             | Röntgenstraße 33, Planegg-<br>Martinsried, GERMANY<br>82152 | Italian     |
| Signature:                         |   |   | Date:       |



# **COMBINED DECLARATION AND POWER OF ATTORNEY**

| Full Name<br>(First, Middle, Last) | Residence Address<br>(City, State, Country) | Post Office Address<br>(Street, City, State, Country) | Citizenship |
|------------------------------------|---|---|-------------|
| Jürgen Kraus                       | Starnberg, Germany                          | Hadorfer Strasse 11 a,<br>Starnberg, GERMANY<br>82319 | German      |
| Signature:                         |   |   | Date:       |

| Full Name<br>(First, Middle, Last) | Residence Address<br>(City, State, Country) | Post Office Address<br>(Street, City, State, Country)      | Citizenship |
|------------------------------------|---|--|-------------|
| Rolf Krauss                        | Planegg-Martinsried,<br>Germany             | Röntgenstraße 7, Planegg-<br>Martinsried, GERMANY<br>82152 | German      |
| Signature:                         |   |  | Date:       |

| Full Name<br>(First, Middle, Last) | Residence Address<br>(City, State, Country) | Post Office Address<br>(Street, City, State, Country) | Citizenship |
|------------------------------------|---|---|-------------|
| Hans Leban                         | Munchen, Germany                            | Radolfzeller Str. 9a<br>Munchen, GERMANY<br>81243     | Austrian    |
| Signature:                         |   |   | Date:       |

| Full Name<br>(First, Middle, Last) | Residence Address<br>(City, State, Country) | Post Office Address<br>(Street, City, State, Country)     | Citizenship |
|------------------------------------|---|---|-------------|
| Wael Saeb                          | Planegg-Martinsried,<br>Germany             | Galileistrasse 6<br>Planegg-Martinsried,<br>GERMANY 82152 | Cyrian      |
| Signature:                         |   |   | Date:       |

# COMBINED DECLARATION AND POWER OF ATTORNEY

| Full Name<br>(First, Middle, Last) | Residence Address<br>(City, State, Country) | Post Office Address<br>(Street, City, State, Country) | Citizenship |
|------------------------------------|---|---|-------------|
| Kristina Wolf                      | Munchen, Germany                            | Margaretenplatz 4<br>Munchen, GERMANY<br>81373        | German      |
| Signature:                         |   |   | Date:       |

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